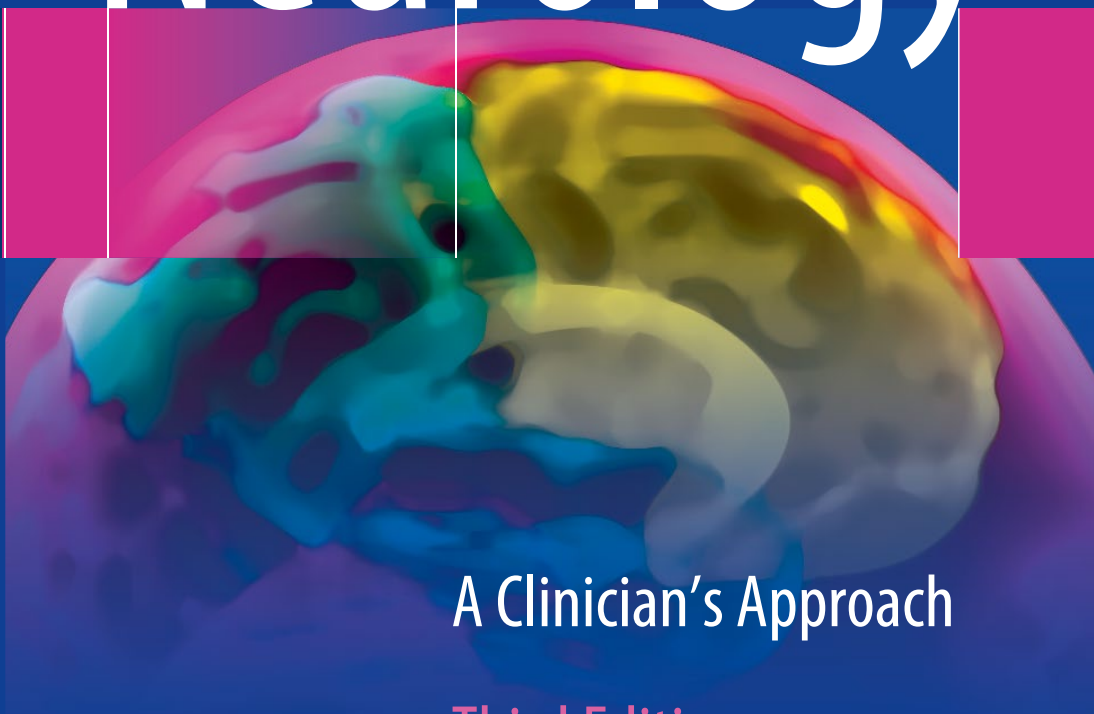
Andrew Tarulli

Neurology



A Clinician's Approach

Third Edition

Springer

Neurology

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To the 1986 New York Mets.

Preface

In the 5 years since the second edition of *Neurology: A Clinician's Approach* was published, much was written about burnout among neurologists. The sources of burnout are debated extensively but the crux of the biscuit is a violation of Newton's Third Law: every action taken on behalf of our patients is countered by an *unequal* and opposite punitive reaction of stultifying documentation, hours spent in insurer phone queues, and misdirected online opprobrium. The ACGME-defined competency of "systems-based practice" has trumped patient care and medical knowledge, to the detriment of doctor and patient alike. David Foster Wallace's masterwork *Infinite Jest* provides my favorite analysis of the problem:

> Chief Steve McGarrett [of 'Hawaii Five-O'] is a classically modern hero of action. He acts out. It is what he does…Captain Frank Furillo of 'Hill Street Blues' is a 'post'-modern hero, a virtuoso of triage and compromise and administration. Frank Furillo retains his sanity, composure, and superior grooming in the face of a barrage of distracting, unheroic demands that would have left Chief Steve McGarrett slumped, unkempt, and chewing his knuckle in administrative confusion.

DFW then wonders:

> But what comes next? What North American hero can hope to succeed the placid Frank? We await, I predict, the hero of non-action, the catatonic hero, the one beyond calm, divorced from all stimulus, carried here and there across sets by burly extras whose blood sings with retrograde amines.

Have we as neurologists devolved to this stage of non-action yet? Will we in the future? Many signs point to yes, but occasionally we can reprise our roles as McGarrett, as heroes of action. We are at our finest and most fulfilled when we sit down with a patient and diagnose them with tools no more complicated than "the hammer and the pin" at our disposal. Clinical skills, the kind taught to me during my residency at Beth Israel Deaconess Medical Center, remain indispensable to patient care and to my personal satisfaction. I thanked my clinical mentors in the two previous editions of *Neurology: A Clinician's Approach* and will repeat my thanks here. Clif Saper, Mike Ronthal, Frank Drislane, Penny Greenstein, Seward Rutkove, Beth Raynor, Rachel Nardin, and Pushpa Narayanaswami – thank you again and always.

Writing *Neurology: A Clinician's Approach* has helped me combat burnout. In this third edition, therefore, I would like to thank my writing mentors – mostly in the form of sentence fragments! My mother and first writing teacher, Marianne, for teaching me to hold a pencil and later for making sure that my junior high school compositions weren't muddled. My father, Joe, for making me write the truth and ensuring that I had the *Bank Street Writer* and a Star SG-10 printer to do so. My brother, Matt, for inspiring me with the single greatest sentence in the English language: "the hilarity of me is great." My wife, Sue, for supporting me and unfailingly protecting my time to write every Saturday and Sunday morning. My daughter, Maddie, for writing stories of a creativity rivaled only by George Saunders. My writing teachers at I.S. 7, Tottenville High School, and New York University: Mr. Kilcommons, Mrs. Hooper, Mr. Hofferman, Mr. Brouder, Mr. Rainey, Mr. Rivkin, Mr. Shatzman, and Alfie Guy. Deirdre McCloskey who in *Economical Writing* (a guide as valuable as Strunk and White) introduced me to Quintilian's aspiration "to write not merely so that the reader can understand but so that he cannot possibly misunderstand." Finally, my team at Springer for helping me complete the third edition of *Neurology: A Clinician's Approach.*

Summit, NJ, USA Andrew Tarulli
June 6, 2020

Contents

Confusion

1

History

Confusion is a cognitive disorder characterized by loss of the normal coherent stream of thought or action [1]. Up to 50% of older hospitalized patients will develop an acute confusional state, and those who become confused are at greater risk for prolonged hospitalization and death [2]. Unfortunately, the confused patient cannot provide a reasonable account of their problem, and detailed narrative histories from family members, nurses, and primary physicians are often similarly unhelpful. The history may consist only of a single phrase such as "they're agitated," "they're not waking up," or "they're confused." Sometimes the history is comprised of examples of abnormal behavior. In many cases, especially when the physician requesting the consult does not know the patient very well, the history is summarized as nothing more than the ambiguous catch-all term "change in mental status."

The three variations of confusion are agitated delirium, somnolence, and incoherence. Despite their strikingly different phenotypes, the shared neuroanatomical cause of all three states is a disturbance in the attentional matrix.

Agitated Delirium

Agitated delirium is characterized by hyperactivity, and aggression and is the most disruptive form of confusion. Patients with agitated delirium scream, yell, rip out intravenous catheters, and sometimes assault hospital staff or even other patients. They are often physically and chemically restrained or undergoing psychiatric evaluation by the time a neurologist is consulted.

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Somnolence

Somnolent patients are sleepy and difficult to arouse. While this form of confusion is less disruptive to the hospital staff and other patients than agitated delirium, somnolence may be more serious, sometimes portending coma. These patients, therefore, require immediate medical and neurological attention.

Incoherence

Incoherence lies between agitated delirium and somnolent confusion on the arousal spectrum. These patients are neither aggressive nor sleepy but lack the ability to think, speak, or act in a lucid, goal-directed manner [1]. Incoherent patients misidentify people and misinterpret situations, especially the circumstances of their hospitalization. They are easily distracted by novel but trivial stimuli and are inattentive to important ones.

Examination

Inattention

The signature mental status abnormality of the confused patient is inattention. This may become obvious with simple observation or when listening to the patient attempt to relate their history. Several bedside tests may help to establish inattention in patients with more subtle deficits:

Months of the Year Backwards

This is perhaps the best bedside test of attention, as it allows both description and quantification of deficits. Normal people should be able to recite the months of the year backwards in 10–15 seconds without error. When asked to recite the months of the year backwards, the confused patient may respond in one of several ways. Agitated patients may erupt in anger at the request to perform such a silly task. Somnolent patients will give no response and fall quickly to sleep. Incoherent patients may begin by starting with December, placing November and October in the correct sequence, and then losing track of the task. Some may stop completely, while others may resume by reciting the months in forward order. Still others may start with December and, when they reach November, start to talk about Thanksgiving. Patients with only subtle inattention may make no mistake other than transposing or stopping briefly to consider the order of the months in the May-April-March sequence.

Reverse Digit Span

Digit span is another useful, quantifiable test of attention. To perform this test, first recite a list of random numbers at a rate of one digit per second and then ask the

patient to repeat the list to you *in sequence*. After establishing the forward digit span, ask the patient to recite a different number sequence backwards. Normal digit spans are at least seven forwards and five backwards.

Serial Sevens

Test serial sevens by asking the patient to subtract 7 from 100 and then 7 from that result and so on until they can subtract no more. This test of attention is somewhat dependent on the patient's educational background and mathematical aptitude and is therefore less useful or quantifiable than testing the months of the year backwards or the reverse digit span.

Spelling "World" Backwards

Spelling "world" backwards is a popular test of attention but is generally not very useful, as the only common mistake is transposing the letters "l" and the "r," an error which is due to chance almost as often as it is to inattention.

Other Changes in Mental Status

In addition to the primary disturbance in attention, confused patients often demonstrate other mental status examination abnormalities including problems with language, memory, and praxis (Chaps. 3 and 4). Careful testing, however, shows that the main problem is inattention.

Asterixis

Asterixis accompanies most metabolic and some structural encephalopathies Despite its common association with hepatic encephalopathy, asterixis is not pathognomonic for this disorder. To test for asterixis, ask the patient to elevate their pronated arms and extend their wrists in front of them as if they are making stop signs. After a latent period of up to 30 seconds, both hands will drop forward slightly and then jerk backwards several times, quickly and asynchronously [3]. These movements are accompanied by tiny oscillations of the fingers. After several jerks, the movements disappear, only to reappear a few seconds later.

Differential Diagnosis

There are several conditions that are often "confused with confusion." Most prominent among these are aphasia, neglect, transient global amnesia, psychosis, and Charles Bonnet syndrome.

Aphasia

Aphasia is an acquired disorder of language resulting from brain damage (Chap. 3). It may be difficult to distinguish some patients with aphasia, particularly those with fluent varieties, from patients with acute confusional states. Patients with Wernicke aphasia, for example, may appear confused because they produce a copious verbal output that makes little sense and because they do not appear to understand simple instructions. Confusion is best distinguished from aphasia by the more widespread pattern of behavioral abnormalities outside of the language domain.

Neglect and the Right Hemispheric Syndrome

Neglect is a multidomain disorder of focused attention [4]. The syndrome is seen most often in patients with right middle cerebral artery infarction or another large right hemispheric lesion and when fully formed is often accompanied by left hemiparesis or hemiplegia. Many of the behaviors of a patient with neglect described here are quite unusual, and it is easy to see why those unfamiliar with the condition would misidentify the patient as being confused.

Visual Neglect

Visual neglect usually is the most striking behavioral feature of the right hemispheric syndrome. The patient with severe neglect looks exclusively to the right side of space and may not respond to the examiner if approached from the left. Specific testing may be required to elicit neglect in patients with more subtle deficits. For example, patients with neglect will describe fewer details of a complex visual scene. They will also have difficulty with line bisection. To perform this test, place an 8–1/2″ × 11″ piece of blank paper in landscape orientation before the patient. Draw a line across the page from left to right and instruct the patient to bisect the line. Normal subjects will come within a few millimeters of the center of the line, but the patient with neglect will bisect it to the right of the midline, sometimes within a few centimeters of the line's right side (Fig. 1.1). Target cancellation is another useful test of hemineglect. Write the letter "A" in a random distribution approximately 15–20 times on a blank sheet of paper in landscape orientation (Fig. 1.2). Make sure to distribute the target letter evenly on the left, right, center, top, and bottom. Next, surround the target with randomly chosen letters of the alphabet and instruct the patient to circle only the letter "A." The patient with neglect will circle the targets predominantly or even exclusively on the right side of the page.

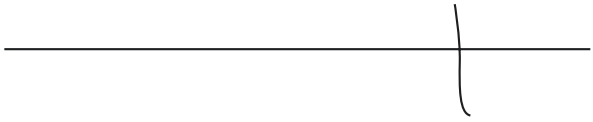

Fig. 1.1 Line bisection test in a patient with neglect. Note that the line is bisected well to the right of midline

Fig. 1.2 Template for the "A" cancellation task. The patient is instructed to circle the target letter "A." Patients with neglect will begin on the right side of the page and may completely ignore the left side

Somatosensory Neglect

To test for somatosensory neglect, first make sure that gross touch perception is preserved on both the left and right sides of the body, as somatosensory neglect cannot be diagnosed if basic sensation is impaired. Instruct the patient to close their eyes and gently stroke the dorsal surfaces of both hands. Patients with neglect will acknowledge only the sensation of being touched on the right hand, a phenomenon known as double simultaneous extinction.

Other Elements of the Right Hemispheric Syndrome

Patients with the right hemispheric syndrome are usually not aware of their deficits or deny them explicitly, a phenomenon known as anosognosia. When asked why they are in the hospital, patients with the right hemispheric syndrome may deny that they are in the hospital. Even when confronted with incontrovertible evidence that they are sick and in the hospital, the patient may continue to deny their illness or express a lack of concern about the problem (anosodiaphoria). Patients with the right hemispheric syndrome tend to speak in monotone because prosody, the rhythmic and melodic elements of speech, is largely a function of the right hemisphere.

Transient Global Amnesia (TGA)

TGA is a sudden-onset temporary disorder of memory encoding that often prompts consultation for confusion. Without warning, the patient starts to ask questions such

as “How did I get here?”, “What happened?”, and “Where am I?” After being provided with an apparently satisfactory explanation, the patient repeats the same questions a few minutes later. The typical patient is otherwise attentive and comports themselves normally. They are capable of the entire spectrum of complex behaviors, including the ability to drive themselves home during an episode. TGA typically lasts for several hours and then resolves, though subtle deficits may persist for days afterwards. The precise etiology of TGA is unclear, with seizure, migraine, and stroke implicated as possible etiologies [5]. Neuroimaging studies are usually normal at the time of the event, though diffusion-weighted MRI abnormalities in the hippocampi may be detected 24 to 48 hours after the event [6]. Because TGA resolves on its own, it requires no specific treatment other than reassurance. A small minority will have a recurrence or “symptomatic TGA” secondary to a seizure disorder or ischemia.

Psychosis

Psychosis may closely resemble an acute confusional state. Features that help to differentiate between psychosis and confusion include the better organization and greater consistency of psychotic hallucinations and delusions and the overall preserved level of consciousness and orientation in psychosis [7]. A normal electroencephalogram helps to exclude encephalopathy as the diagnosis in cases that are difficult to distinguish on clinical grounds alone. Formal psychiatric assessment may help to differentiate between the two if any doubt remains.

Charles Bonnet Syndrome

Charles Bonnet syndrome is defined by visual hallucinations that occur in the context of severe visual loss and deafferentation of the visual cortex. The syndrome is most common in older patients with dementia and may be misdiagnosed as a confusional state. The hallucinations are complex and stereotyped, consisting of people, animals, or animated objects. Usually the hallucinations are not threatening to the patient, but in some instances they are disturbing and lead to agitation. The symptoms may come on suddenly and may wax and wane. Unfortunately, effective treatments are lacking because the visual loss is severe and uncorrectable. Reassurance that the hallucinations do not represent serious psychiatric illness may help patients with milder, non-distressing symptoms, but those with more bothersome symptoms may benefit from treatment with antipsychotic medications.

Table 1.1 Diagnostic testing for confusion

Test	Diagnosis
Complete blood count	Infection
Basic metabolic panel	Hyponatremia Hyperglycemia Hypoglycemia Hypercalcemia
Liver function tests, including ammonia	Hepatic encephalopathy
Arterial blood gas analysis	Hypoxia Hypercarbia
Thyroid function tests	Hyperthyroidism Hypothyroidism
Urinalysis	Urinary tract infection
Serum and urine toxicology screen	Intoxication with alcohol, cocaine, opioids, barbiturates, or benzodiazepines
Chest X-ray	Pneumonia
Non-contrast head CT	Subdural hematoma Intracranial hemorrhage Space-occupying lesion Subarachnoid hemorrhage
Head MRI	Acute ischemic stroke Encephalitis Posterior reversible encephalopathy syndrome
Electroencephalogram	Nonconvulsive status epilepticus
Lumbar puncture	Bacterial meningitis Viral meningitis and encephalitis Subarachnoid hemorrhage Neoplastic meningitis Fungal meningitis Paraneoplastic encephalitis

Diagnostic Testing

The source of confusion often can be identified from a complete medical history, medication list review, and chart review. Table 1.1 contains a basic guide to additional diagnostic testing for some of the more common disorders that produce confusion. Many of these tests are ordered routinely in all hospitalized patients, and there are just a few additions specifically for the confused patient. Electroencephalography (EEG) may help to confirm that a patient is encephalopathic (see Figs. 1.3 and 1.4) if any doubt remains after the history and physical examination. EEG is also useful for determining whether a patient is in nonconvulsive status epilepticus. Almost all confused patients should undergo a neuroimaging study. Generally, a non-contrast head CT is sufficient to exclude the possibility of a structural lesion, particularly subdural hematoma. Brain MRI may be needed when acute stroke or inflammatory lesions are suspected. Finally, lumbar puncture may be indicated when an infectious, inflammatory, or neoplastic process is suspected.

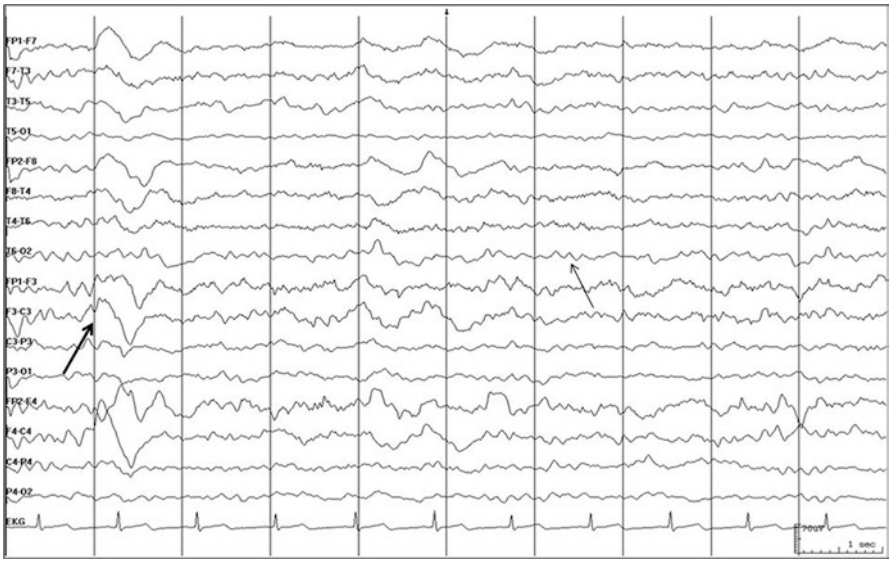

Fig. 1.3 EEG in patient with moderate encephalopathy. Posterior dominant rhythm (thin arrow) is approximately 5–6 Hz. There is also superimposed generalized slowing (thick arrow). (Image courtesy of Dr. Julie Roth)

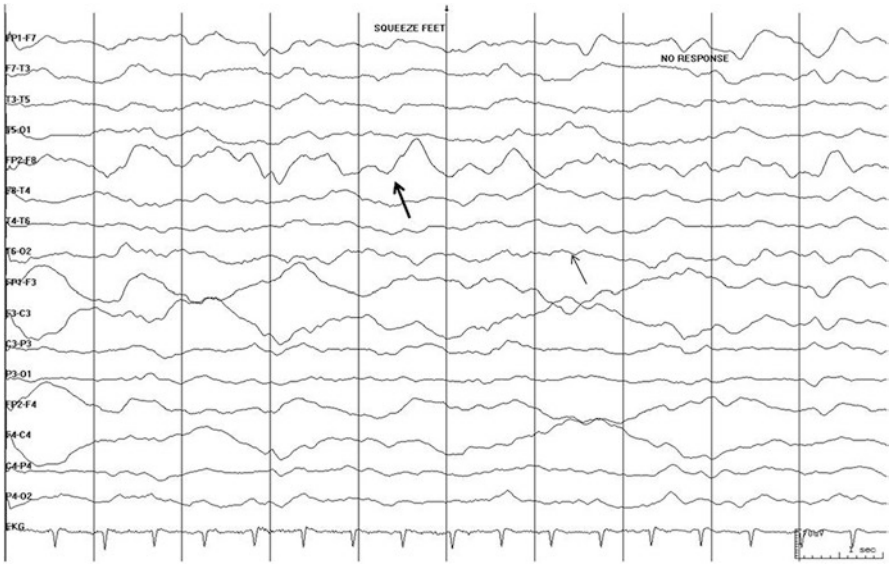

Fig. 1.4 EEG in patient with severe encephalopathy. Posterior dominant rhythm (thin arrow) is approximately 2–3 Hz. Additional slowing is noted throughout the record (thick arrow). There is no reactivity of the EEG to a request for movement. (Image courtesy of Dr. Julie Roth)

Etiologies

Toxic and Metabolic Encephalopathies

Medical diseases and intoxications are the most common causes of the acute confusional state. While essentially any medical disturbance may lead to confusion, commonly identified precipitants include urinary tract infections, pneumonia, hyponatremia, uremia, hepatic dysfunction, hypoxia, and hypercarbia (Table 1.1). In many elderly patients, subtle rather than overt metabolic derangements are responsible for the problem. Among the medications that lead to confusion, the most common culprits are opioids, benzodiazepines, sleeping aids, and anticonvulsants. Intoxication with drugs of abuse is another important cause of confusion. While the various toxic and metabolic encephalopathies are quite similar in their presentations, those related to ethanol consumption and hepatic failure present in distinctly different fashions, and I will therefore discuss them in more detail here.

Ethanol and Confusion

Ethanol Intoxication

The signs of acute ethanol intoxication are easily identifiable and include slurred speech, incoherence, and ataxia. If there is any doubt about the diagnosis, it may be confirmed by finding an elevated serum ethanol level.

Ethanol Withdrawal

Withdrawal symptoms may develop as soon as 6 hours after stopping heavy alcohol intake. The most common manifestation of ethanol withdrawal is tremulousness. When ethanol withdrawal causes a confusional state, it most frequently takes the form of agitated delirium, including auditory and visual hallucinations. These typically peak between 24 and 36 hours of ethanol withdrawal [8]. Delirium tremens is characterized by confusion plus autonomic instability including diaphoresis, hypertension, and tachycardia. It develops between 2 and 4 days after ethanol discontinuation. If not treated properly, delirium tremens may be fatal. Benzodiazepines, administered on a standing basis or as needed for signs of severe withdrawal (Table 1.2), are the agents of choice in reducing the morbidity of ethanol withdrawal, but they should be used cautiously in patients with liver disease [9].

Table 1.2 Benzodiazepine regimens for ethanol withdrawal

	Standing regimen	PRN regimen
Lorazepam	2 mg q6h × 24 hours followed by 1 mg q6h × 48 hours	2–4 mg q1h prn agitation or autonomic instability
Diazepam	10 mg q6h × 24 hours followed by 5 mg q6h × 24 hours	10–20 mg q1h prn agitation or autonomic instability
Chlordiazepoxide	50 mg q6h × 24 hours followed by 25 mg q6h × 48 hours	50–100 mg q1h prn agitation or autonomic instability

Wernicke Encephalopathy

Chronic alcoholism and malnutrition may lead to thiamine deficiency and the clinical syndrome of Wernicke encephalopathy. The classic clinical triad of Wernicke encephalopathy is confusion, ophthalmoplegia, and ataxia. Because the triad is complete in only a minority of patients with Wernicke encephalopathy, it is good practice to administer thiamine 100 mg intravenously tid for 3 days to any confused patient unless another source is identified [10]. Thiamine is a benign intervention, and if Wernicke encephalopathy is not treated promptly, the syndrome may be irreversible. Intravenous thiamine leads to variable improvement in ocular symptoms in hours to days and ataxia and confusion in days to weeks [8].

Hepatic Encephalopathy

Both acute and chronic liver failure produce neurologic dysfunction. In its mildest form, hepatic encephalopathy is characterized by inattention and psychomotor slowing. Deficits may not be detected at this stage unless they are sought specifically. Moderate hepatic encephalopathy produces more prominent inattention and somnolence. Asterixis, the most well-known sign of hepatic encephalopathy, is usually present at this stage. Other features of moderate hepatic encephalopathy include pyramidal and extrapyramidal signs such as dysarthria, tremor, rigidity, and bradykinesia. Patients may have EEG recordings that show triphasic waves, though this finding is not pathognomonic for hepatic encephalopathy and may be seen in any cause of encephalopathy. Advanced hepatic encephalopathy is characterized by seizures and more severe cognitive dysfunction, which may progress to coma and death. Fulminant hepatic encephalopathy with massive transaminitis, often due to intoxication with acetaminophen, may produce malignant cerebral edema and increased intracranial pressure (Chap. 2). While a high serum ammonia level may suggest the diagnosis of hepatic encephalopathy, the substantial overlap between venous ammonia levels and the degree of hepatic encephalopathy makes following serial ammonia levels unhelpful for monitoring disease progression [11]. Treatment of hepatic encephalopathy must start with identification of the precipitating factors including infection, metabolic disturbances, dietary indiscretions, and gastrointestinal bleeding. Once these are identified and corrected, treatment should focus on reducing enteric bacterial ammonia production with the nonabsorbable disaccharide lactulose (30–60 mg tid). If this is not effective within 24–48 hours, then the antibiotic rifaximin (400 mg tid) should be started. Although symptoms may be temporarily reversible, hepatic encephalopathy has a poor long-term prognosis.

Spinal Fluid Pleocytosis

Abnormal cells in the spinal fluid, whether they are neutrophils in bacterial meningitis, lymphocytes in viral meningitis, tumor cells in neoplastic meningitis, or red blood cells in subarachnoid hemorrhage (Chap. 19), may produce an acute confusional state.

Bacterial Meningitis

The typical presentation of bacterial meningitis is fever, headache, and stiff neck. It is often accompanied by a confusional state which is otherwise indistinguishable from other toxic or metabolic encephalopathies. If there is not a high index of suspicion for bacterial meningitis from the outset, the diagnosis will be missed, potentially leading to irreversible neurologic damage or even death. Several findings may suggest bacterial meningitis but have limited sensitivity. Nuchal rigidity, a classical sign of bacterial meningitis, is seen in only about 30% of patients [12]. The Kernig sign is elicited by placing the patient supine with the hip flexed to 90° and looking for resistance or pain upon attempted knee extension. The Brudzinski sign is elicited in a supine patient by observing spontaneous hip flexion when the neck is flexed. Unfortunately, the Kernig and Brudzinski signs are unreliable, as they accompany meningitis in only 5% of cases [12]. If you suspect bacterial meningitis, then you must perform a lumbar puncture, as suggestive clinical signs cannot be relied upon for making or excluding the diagnosis. The technique and safety of lumbar puncture are discussed in Box 1.1. The most important findings in the cerebrospinal fluid of a patient with bacterial meningitis are neutrophilic pleocytosis, elevated protein, and low glucose. Even if all three of these parameters are normal, patients with suspected bacterial meningitis should be treated empirically with antibiotics covering the commonly responsible pathogens *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenza* until Gram stain and cultures return [13, 14]:

- Ceftriaxone 2 g IV q12h (substitute cefepime 2 g q8h in immunocompromised patients).
- Vancomycin 1 g IV q12h.
- Dexamethasone 10 q6h; continue for 4 days if pneumococcal meningitis is identified.

Ampicillin 2 g IV q4h should be added for patients older than 50, because there is a greater risk for infection with *Listeria monocytogenes* in this population. Continue treatment until cultures are negative for 48 hours or a specific bacterium is isolated. Further tailoring of antibiotic therapy depends on the organism cultured and its antibiotic sensitivity and should be determined in consultation with an infectious disease specialist.

Box 1.1 Lumbar Puncture

Many of the causes of confusion require CSF analysis. Although time is of the essence in performing a lumbar puncture for patients with suspected bacterial meningitis, it is first necessary to exclude space-occupying intracranial lesions, especially those in the posterior fossa, which may lead to life-threatening cerebral herniation after lumbar puncture. Not every patient, however, requires a CT scan. Risk factors for space-occupying lesions, and therefore indications for performing a head CT prior to lumbar puncture, include age greater than 60, immunocompromised state, seizures within 1 week prior to presentation, papilledema, or an abnormal neurologic examination (Hasbun et al. 2001). In addition to cerebral herniation, the risks of the procedure include headache (30%), bleeding at the site of the puncture, and infection. If any doubt remains about the safety of lumbar puncture, antibiotics to treat bacterial meningitis should be initiated while waiting for a head CT to be performed.

Lumbar punctures are often technically challenging for junior house staff. The main reason that a lumbar puncture is unsuccessful is that the patient is positioned improperly. Almost all textbooks instruct that the lumbar puncture should be performed in the lateral decubitus position. This position is ideal to obtain an accurate measurement of the cerebrospinal fluid pressure but is also associated with a greater failure rate due to spine rotation and incomplete opening of the targeted intervertebral space. The subarachnoid space is easier to access if the patient sits up and leans forward (Fig. 1.5).

Identify the L2-3 or L3-4 interspace by drawing an imaginary line between the iliac crests as a marker of the L4 interspace. Next, sterilize the area with iodine or other sterilizing agent and place a drape over the back, with a window directly over the area of the planned lumbar puncture site. Infiltrate the target interspace with a small amount of lidocaine. Place the lumbar puncture needle into the space and advance slightly until you feel a slight decrease in resistance or "pop." There is often a series of two pops, a first smaller one and a second larger a few millimeters deeper which indicates success. If measurement of opening pressure is necessary, rotate the patient into the lateral decubitus position, withdraw the stylet, and connect the manometer. Make sure to collect enough spinal fluid to perform all appropriate studies and to use an appropriate fixative solution when performing cytologic examination to look for cancer cells. After all of the fluid is collected, replace the stylet and withdraw the needle. Bed rest in a supine position is often recommended to decrease the risk of headache, though there is little evidence that this is effective.

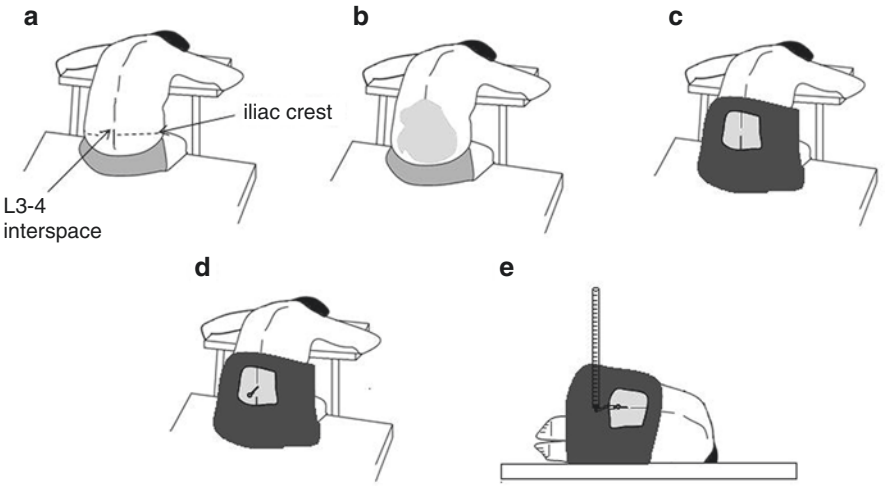

Fig. 1.5 Technique for performing lumbar puncture. Identify the L3-4 interspace as the interspace superior to a line connecting the iliac crests (**a**). Prepare the area with iodine or another sterilizing agent (**b**) and a sterile drape (**c**). After anesthetizing the area with lidocaine or another anesthetic, place the lumbar puncture needle into the L2-L3 or L3-4 interspace (**d**). If pressure needs to be measured, then rotate the patient into the lateral decubitus position, withdraw the stylet, and attach the manometer (**e**). Collect the fluid and send to the laboratory for studies

Viral Meningitis and Encephalitis

Because they present so similarly, it may be difficult to distinguish between bacterial and viral meningitis on clinical grounds alone. Lumbar puncture is often unhelpful in distinguishing the two in the acute setting, as viral meningitis may also cause a neutrophilic pleocytosis in the first 24 hours of infection. Most patients with viral meningitis are treated empirically with antibiotics, while cultures to exclude bacterial meningitis are being performed.

Viral encephalitis is differentiated from meningitis by viral invasion of the brain parenchyma and therefore a greater likelihood of confusion, seizures, and serious neurologic morbidity. The most important causes of viral meningitis and encephalitis are:

- Enteroviruses. Most viral meningitis is due to enteroviral (e.g., coxsackie and echovirus) infection. The incidence of enteroviral meningitis peaks in the summer and early fall and does not require treatment beyond supportive care.
- Herpes simplex virus-1 (HSV-1). HSV-1 produces encephalitis which classically (but not exclusively) affects the temporal lobes. The classical findings of HSV encephalitis including T2-weighted hyperintensities in the temporal lobes on MRI (Fig. 1.6), lateralized periodic discharges on EEG, and red blood cells in the CSF are not universal, especially in the early stages. The only way to make a firm

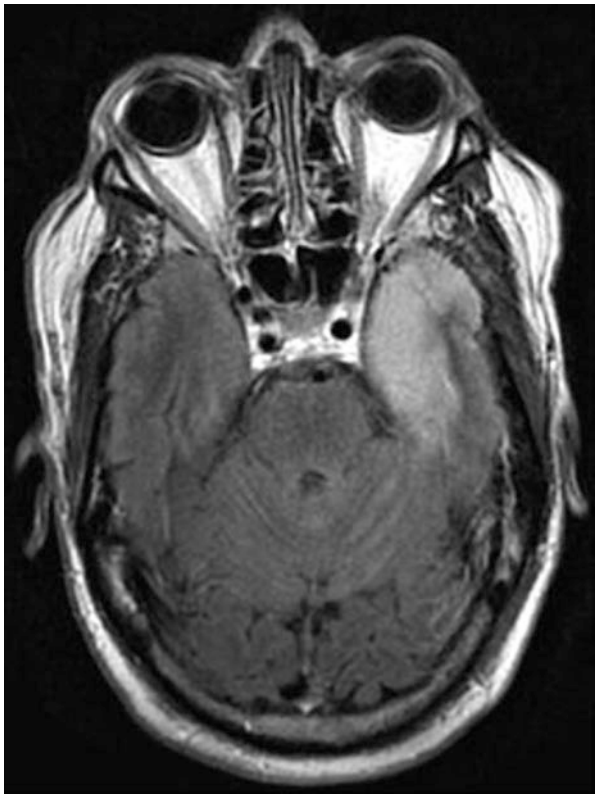

Fig. 1.6 FLAIR MRI of patient with hyperintensity in the left temporal lobe

diagnosis is by finding a positive HSV PCR in the cerebrospinal fluid. Because HSV PCR usually requires several days to process, during which time neurologic deterioration may occur, treat all patients with suspected HSV encephalitis with acyclovir 10 mg/kg tid until the HSV PCR results return as negative. If the HSV PCR is positive, continue treatment for 21 days. Monitor kidney function while treating with acyclovir, as it may cause acute tubular necrosis.

- Herpes simplex virus-2 (HSV-2). Most patients with HSV-2 meningitis have genital herpes at the time of presentation. In the absence of herpetic lesions, the diagnosis is made by finding positive HSV PCR in the CSF. Treat patients with HSV-2 meningitis with intravenous acyclovir, as described for patients with HSV-1 encephalitis.
- Human immunodeficiency virus (HIV). It may be difficult to distinguish HIV seroconversion from other causes of viral meningitis. While patients with HIV seroconversion improve with little more than supportive care, it is important to recognize the pathogen for counseling purposes and for planning further treatment.
- Other viral encephalitides. A variety of viral pathogens cause encephalitis, often serious, and life-threatening. Some of the more important viruses that produce encephalitis include:

- Varicella zoster virus
- Rabies virus
- Eastern equine encephalitis virus
- Western equine encephalitis virus
- St. Louis equine encephalitis virus
- West Nile virus
- Powassan virus

Neoplastic Meningitis/Leptomeningeal Metastasis

Tumor cells that invade the cerebrospinal fluid and leptomeninges have the potential to cause multifocal dysfunction of the central nervous system, cranial nerves, and nerve roots. The constellation of symptoms may include encephalopathy, headaches, seizures, increased intracranial pressure, diplopia, dysarthria, radicular pain, and weakness. The most common tumors that produce neoplastic meningitis are primary CNS tumors, carcinomas of the lung and breast, melanoma, lymphoma, and leukemia [15]. Although neoplastic meningitis usually accompanies advanced cancer, it may be the first sign of disease in some patients. CSF examination may show a high cell count with lymphocytic predominance and a high protein, although routine studies are occasionally normal. A positive cytologic examination of the CSF establishes the diagnosis. Malignant cells are found after a single lumbar puncture in approximately 55% and after a second lumbar puncture in 85% [16]. Three or more lumbar punctures, each with 10 mL CSF sent for cytologic evaluation, should be performed if the clinical suspicion for neoplastic meningitis is high. Flow cytometry is more sensitive in identifying leptomeningeal metastasis in patients with hematologic malignancies, with a sensitivity of 73%, compared to 32% with conventional cytologic testing in one study [17]. Contrast-enhanced MRI serves an adjunctive role in diagnosis, showing leptomeningeal enhancement and focal nodular tumor deposits in about half of high-risk patients with initially normal cytologic examinations [18]. MRI is more likely to show evidence for leptomeningeal metastasis in patients with solid tumors than in those with hematologic malignancies [19]. If possible, perform MRI prior to lumbar puncture, as lumbar puncture itself may lead to artifactual leptomeningeal enhancement. Neoplastic meningitis is a poor prognostic sign, associated with a median survival of less than 6 months [15]. In most cases, therapy is supportive. Steroids and local radiation are used for palliative purposes. Intrathecal or systemic methotrexate or cytarabine may improve survival by a few months [15].

Lyme Meningitis

Infection with the tick-borne spirochete *Borrelia burgdorferi* produces Lyme disease, a disorder with protean neurologic and systemic manifestations. Neurologic symptoms of early disseminated Lyme disease occur several weeks to months after tick bite and may include radiculopathy, facial palsy, or lymphocytic meningitis. There is often no history of the characteristic *erythema chronicum migrans* rash, an erythematous rash, classically associated with central clearing (“bullseye pattern”), which typically appears between 1 and 2 weeks after a tick bite. The diagnosis is

established by finding *Borrelia* antibodies in the CSF. Serologic confirmation is made first with enzyme-linked immunosorbent assay (ELISA) test and then a confirmatory Western blot. In many patients, however, antibodies are absent at presentation, and the diagnosis is made only from the relevant clinical and exposure history. Treat Lyme meningitis with ceftriaxone (2 g IV qd for 14–28 days).

Tuberculous Meningitis

Tuberculous meningitis is a potentially devastating condition that typically develops subacutely over a few weeks with a prodrome of generalized malaise, low-grade fever, and weight loss. Neurologic manifestations are rarely limited to meningitis and also include hydrocephalus, vasculitis with stroke, tuberculomas, and cranial nerve palsies. Rapid progression to loss of consciousness and coma occurs in untreated patients. CSF characteristically shows an elevated opening pressure with very high protein and very low glucose levels. In patients without known tuberculosis, diagnostic testing including CSF acid-fast bacilli, mycobacterial culture, and tuberculosis polymerase chain reaction (PCR) has only modest sensitivity [20]. Multiple lumbar punctures may be required before finding a positive result. Systemic examination (chest X-ray, induced sputum, etc.) also is of low yield. Tuberculous meningitis requires aggressive treatment: usually a four-drug regimen (isoniazid, pyrazinamide, rifampin, and ethambutol) is employed. Because drug resistance is very common and changes periodically on both local and global scales, an infectious disease specialist should always be consulted.

Fungal Meningitis

Coccidioides immitis produces a lymphocytic meningitis endemic to the American Southwest. The diagnosis is made by culturing the organisms or by finding coccidioidal antibodies in the CSF. Treat patients with coccidioidal meningitis with oral fluconazole (400 mg qd) for 3–6 months.

Cryptococcus neoformans may produce a life-threatening meningitis which is seen mostly in immunocompromised patients. CSF shows a monocytic pleocytosis, which is often modest in patients who cannot mount a robust immune response. Cryptococci stain positively with India ink. Treat cryptococcal meningitis with a combination of amphotericin B IV 1 mg/kg qd and flucytosine PO 100 mg/kg qd for 2 weeks [21]. Additional treatment should be determined in conjunction with an infectious disease specialist.

Limbic Encephalitis

Limbic encephalitis is an immune-mediated neurological syndrome characterized by subacutely progressive confusion, memory loss, and seizures. It classically occurs as a paraneoplastic syndrome, in many cases presenting before a cancer diagnosis, but also occurs as a non-neoplastic, autoimmune process. The various encephalitides are named for associated autoantibodies, though in many cases the antibody is not directly pathogenic but rather a marker of autoimmunity. The two antibody syndromes most closely associated with limbic encephalitis are anti-Hu (also known as anti-neuronal nuclear antibody-1, ANNA-1) antibody syndrome and

anti-NMDA receptor encephalitis. Anti-Hu limbic encephalitis is seen most often in patients with small cell lung cancer, while the anti-NMDA receptor syndrome is most closely associated with ovarian teratomas in young women [22, 23]. Patients with anti-NMA receptor encephalitis often have neuropsychiatric changes such as aggressive or psychotic behaviors and autonomic dysfunction. Other paraneoplastic syndromes, some described in only small case series, associated with limbic encephalitis include:

- Anti-Ma2 associated with testicular cancer in young men [22]
- Anti-CV2/CRMP5 associated with small cell lung cancer [23]
- CASPR2 (contactin-associated protein-like 2) antibodies, sometimes associated with polyneuropathy, neuromyotonia, and peripheral nerve hyperexcitability [24]
- LGI1 (leucine-rich, glioma-inactivated 1) antibodies associated with faciobrachial dystonic seizures [25, 26]
- $GABA_A$ receptor, which is usually not associated with an underlying neoplasm [27]
- $GABA_B$ receptor, which is most often associated with small cell lung cancer [28]
- AMPA receptor, in patients with carcinoma of the lung, breast, or thymus [29]

Both serum and CSF should be tested for these autoantibodies, as they offer complementary information [30]. It is important to recognize that commercial antibody tests are not yet available for all of the causes of limbic encephalitis. MRI of the brain characteristically shows T2 hyperintensity in the medial temporal lobes. In patients with suspected paraneoplastic antibody syndromes, evaluation should include a thorough investigation for a primary tumor including torso CT and PET scan [31]. Often, the tumor is quite small and requires dedicated, high-resolution imaging of the target organ. Limbic encephalitis may improve with successful treatment of the underlying cancer, though it is often challenging to convince a surgeon or oncologist to address what would otherwise look like an inconsequential mass. Most patients with paraneoplastic limbic encephalitis will require additional immunotherapy including intravenous immunoglobulin and plasmapheresis or immunosuppressants including corticosteroids, cyclophosphamide, or rituximab [32, 33].

Drug-Induced Meningitis

The most common causes of drug-induced meningitis are nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole, and intravenous immunoglobulin. These agents usually produce a neutrophilic pleocytosis in the acute setting. Drug-induced meningitis resolves when the offending agent is withdrawn.

Nonconvulsive Status Epilepticus (NCSE)

NCSE is defined as uninterrupted complex partial or absence seizures that last for at least 30 minutes. The behavior of a patient in NCSE differs little from that of a patient with any of the more common toxic or metabolic sources of confusion, so

maintaining a high index of suspicion for NCSE is important. The best way to confirm the diagnosis is by finding ongoing seizures on EEG; continuous video-EEG monitoring is particularly useful for this application. There are many times, however, when EEG is not readily available, in which case empiric treatment with 2 mg of intravenous lorazepam may disrupt NCSE and improve the confusional state. Compared to convulsive status epilepticus (Chap. 20), NCSE poses a lower risk for brain damage and is not a life-threatening emergency. It is not clear, therefore, how aggressively NCSE should be treated. While small doses of benzodiazepines and initiating or augmenting maintenance doses of anticonvulsants are an appropriate initial approach, drastic measures such as sedatives or pentobarbital infusions may do more harm than good. The decision to proceed with aggressive pharmacologic treatment of NCSE should be decided on a case-by-case basis, bearing in mind that the ultimate prognosis of NCSE is related to the process responsible for the seizures and not to the seizures themselves.

Structural Lesions Responsible for Confusion

Because of their rarity, it is easy to become cavalier and dismiss the possibility of a focal structural lesion as a source of confusion. Subdural hematoma is the diagnosis that is most often missed. Usually caused by traumatic tearing of the bridging subdural veins, subdural hematoma may result in various neurological presentations including hemiparesis, seizures, headaches, and confusion. The head trauma that produces a subdural hematoma is often trivial and sometimes not remembered by the patient. Thus, it is almost mandatory to obtain a non-contrast head CT in every confused patient (see Chap. 21, Fig. 21.3). Most subdural hematomas reabsorb without intervention, but progressive neurologic deficits or radiographic evidence of hematoma expansion require surgical intervention. Although ischemic stroke is not a common cause of confusion, left posterior cerebral, right middle cerebral artery, and caudate infarctions may produce confusional states [34–36].

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is a severe encephalopathy produced by vasogenic edema [37]. The clinical syndrome may be quite variable but usually takes the form of a rapidly developing encephalopathy accompanied by visual disturbances and sometimes by seizures. The most common precipitants are extreme hypertension (especially when it develops rapidly), eclampsia, and calcineurin inhibitors used as immunosuppressants after organ transplantation such as tacrolimus and cyclosporine. Characteristic imaging findings in PRES are T2 hyperintensities (best visualized using fluid-attenuated inversion recovery sequences) with a predilection for the subcortical white matter of the parietal and occipital lobes (Fig. 1.7). Despite its name, PRES is not necessarily restricted to the posterior part of the brain and may not be reversible: the frontal lobes, thalamus, and basal ganglia may be involved, and PRES may be

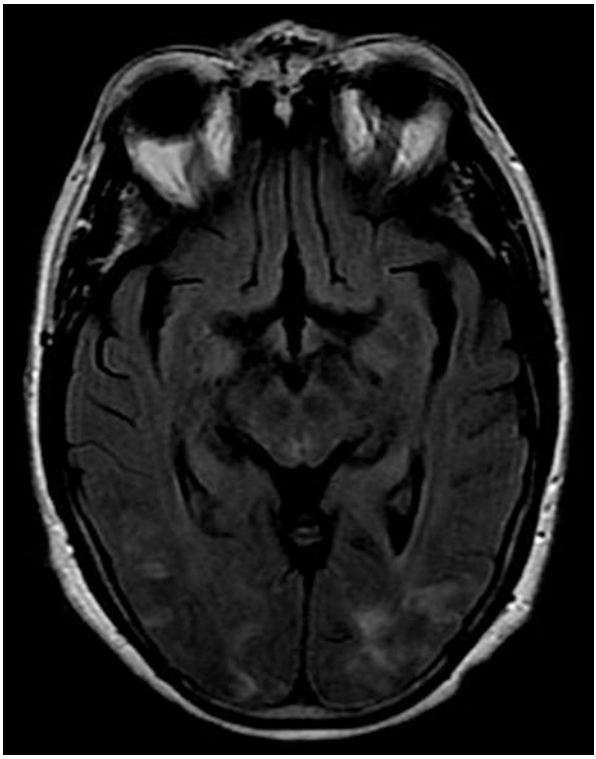

Fig. 1.7 FLAIR MRI of a patient with posterior reversible encephalopathy syndrome (PRES) showing the characteristic occipital lobe hyperintensities

associated with poor neurologic outcome and even death. Blood pressure correction (most commonly with a regimen including a calcium channel blocker), delivery of the baby for women with eclampsia, and discontinuation of calcineurin inhibitors may help to resolve PRES.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potential neurologic emergency that occurs in patients who take dopamine antagonists or who withdraw rapidly from levodopa or dopamine agonists. High-potency antipsychotics pose the greatest risk, but low-potency and atypical antipsychotics and the antiemetic metoclopramide may also cause NMS. Symptoms tend to occur in patients who have just started antipsychotics or who have undergone a rapid increase in dose. The core clinical features are agitated delirium, rigidity, autonomic instability, and hyperthermia. Massive, life-threatening rhabdomyolysis may occur. Treatment in an intensive care unit with careful attention to cardiopulmonary support is usually necessary. The responsible agent should be discontinued. The skeletal muscle relaxant dantrolene (1–2.5 mg/kg IV, up to 10 mg qd) should be given to patients with extreme rigidity. The dopamine agonist bromocriptine (2.5 mg q6h) should also be used to reverse dopamine receptor blockade. Hyperthermia,

autonomic instability, and renal failure must also be addressed. After NMS has resolved, most patients will need to restart neuroleptics for their underlying psychotic disorder: these can be resumed several weeks later, with lower-potency or atypical agents being preferred to higher-potency ones.

General Approach to Treatment

Most acute confusional states have an identifiable and often a reversible cause. It is essential to ensure that no more harm comes to the patient while the responsible abnormality is being corrected. This is best accomplished by providing the patient with a room of their own, soft lighting, and the company of a family member or friend. Many patients, particularly elderly ones, will require chemical or physical restraints, which must be administered judiciously. Quetiapine (25 mg prn) is perhaps the best tolerated antipsychotic medication for sedating combative patients. Haloperidol (0.5–1 mg IV) may be used for patients who refuse or cannot take oral medications. Benzodiazepines are effective sedatives but should be avoided if possible. Valproic acid is helpful for patients in whom antipsychotics and benzodiazepines are contraindicated. Security sitters and physical restraints may be necessary for extremely agitated patients.

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Coma and Related Disorders

2

History

Coma is a state of eyes-closed unresponsiveness in which even the most vigorous stimulation fails to arouse the patient [1]. Because comatose patients cannot communicate, the history must be assembled from family members, emergency service records, and hospital notes. Clues to the etiology of coma obtained from the history include the presence of trauma, evidence of intoxication, and history of cardiac, pulmonary, hepatic, and renal disease. The tempo of coma onset may also be helpful: sudden onset in the absence of trauma favors a cardiogenic source or intracranial hemorrhage, whereas gradual onset is more consistent with a metabolic cause or a slowly expanding mass lesion. In many cases the history contains few details beyond the patient being "found down," and the evaluation of the comatose patient quickly shifts to neurological examination and diagnostic testing.

Examination

Mental Status Examination

The purpose of the mental status examination of the comatose patient is to verify that they are actually comatose rather than merely encephalopathic. Before beginning the examination, make sure to discontinue any short-acting sedatives such as midazolam or propofol. By definition, a comatose patient's eyes should be closed, and they should appear as if they are sleeping. If gently calling out their name does not produce any response, then yell out their name or gently squeeze their hand. Attempt to awaken them with increasingly noxious stimuli: severely encephalopathic patients may respond to painful maneuvers such as rubbing the sternum, applying nailbed pressure, or pinching the areola, whereas comatose patients will not. Document the reaction to each stimulus and also note what happens when it is withdrawn.

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Pupillary Reactions

Abnormal pupillary reactions may provide insight into structural causes of coma involving the thalamus and brainstem. Asymmetric pupils suggest structural lesions. In most cases, symmetric pupils indicate a metabolic source of coma, but there are several important bilaterally symmetric structural lesions that preserve pupillary symmetry and must not be missed. Pre-existing pupillary irregularities, such as those that might be due to prior cataract surgery, must be excluded before assigning too much weight to an abnormal pupillary examination. Chapter 7 contains a more detailed discussion of pupillary neuroanatomy and function. The following patterns of pupillary reactions are the most important in comatose patients:

1. Normal size pupils with normal reactions (Fig. 2.1a). This pattern suggests a toxic or metabolic disturbance.
2. Small, reactive pupils (Fig. 2.1b). Small, reactive pupils are more likely secondary to toxic or metabolic disturbances, though they may also be produced by thalamic lesions.
3. Unreactive midsize pupils (Fig. 2.1c). Midbrain lesions produce unreactive midsize pupils. More commonly, however, this pattern is the result of toxic or metabolic disturbances.

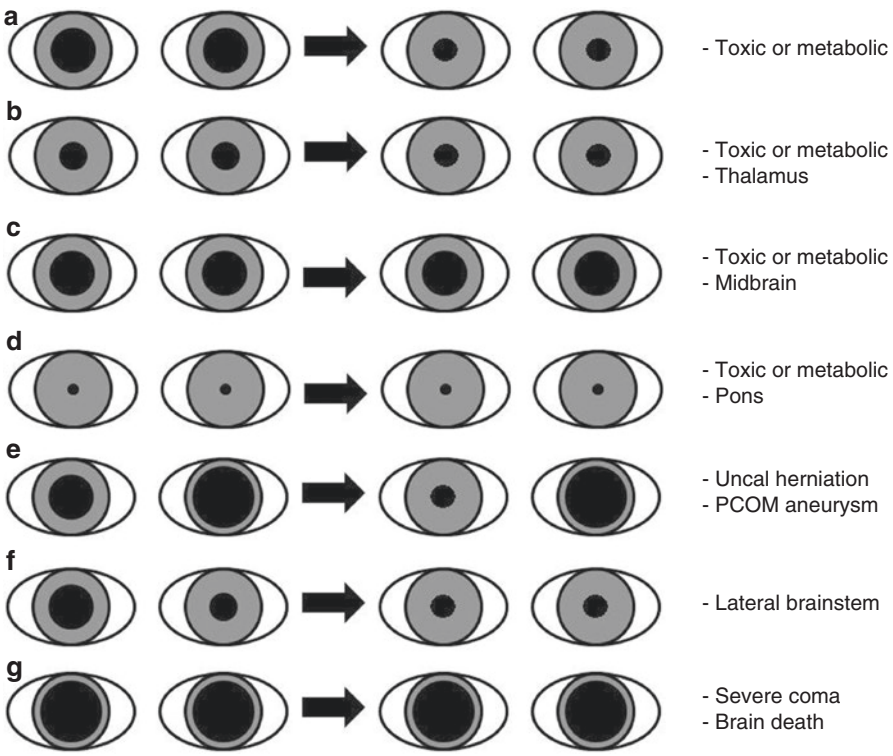

Fig. 2.1 Pupillary reactions in coma. See text for details

4. Unreactive pinpoint pupils (Fig. 2.1d). Pontine lesions classically produce pinpoint pupils. Opioid intoxication is another important source of pinpoint pupils, though trace reactivity may be maintained.
5. Asymmetric pupils, abnormal pupil is dilated (Fig. 2.1e). The most common causes of this pattern in comatose patients are uncal herniation and a ruptured posterior communicating artery aneurysm. Both conditions are true neurologic emergencies that require rapid evaluation and treatment.
6. Asymmetric pupils, abnormal pupil is constricted (Fig. 2.1f). Coma accompanied by Horner syndrome points to lateral brainstem damage.
7. Fixed and dilated pupils (Fig. 2.1g). This pattern suggests severe coma or brain death but is not helpful in defining the cause.

Blink Reflexes

The sensory arc of the blink reflex originates in the cornea and travels in the ophthalmic branch of the trigeminal nerve (Fig. 2.2). These trigeminal nerve fibers synapse in the ipsilateral principal sensory nucleus of the trigeminal nerve and the nucleus of the spinal trigeminal tract in the pons and medulla. Neurons originating

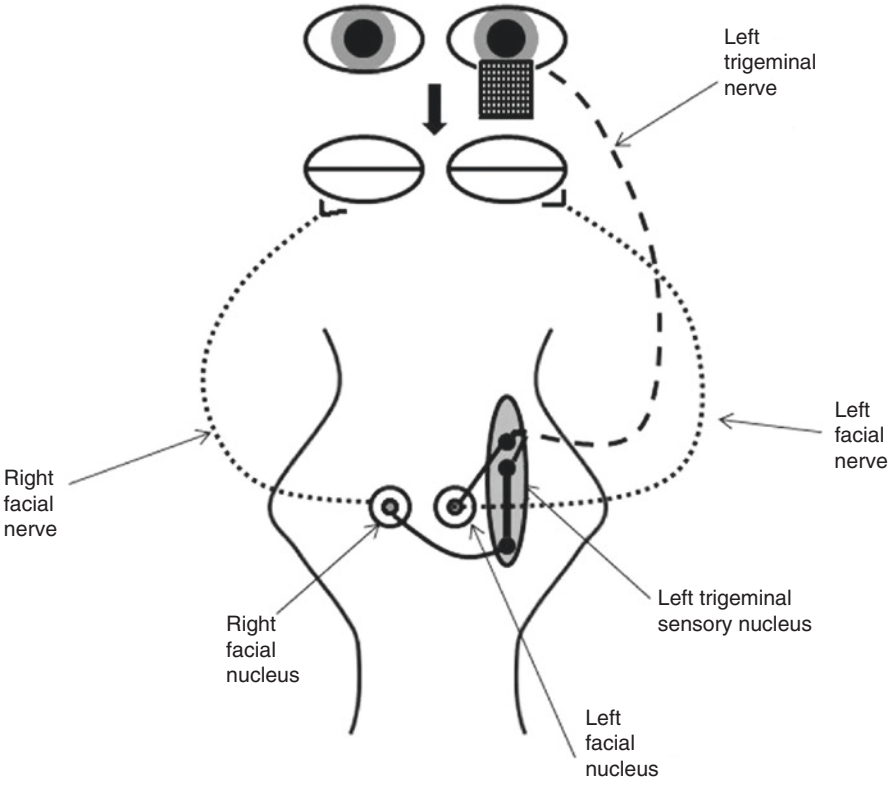

Fig. 2.2 Schematic of the blink reflex. See text for details

from these trigeminal nuclei send axons to both the ipsilateral and contralateral facial nuclei. The facial nucleus gives rise to the facial nerve which innervates the ipsilateral orbicularis oculi, contraction of which produces blinking.

To assess the corneal reflex in a comatose patient, peel both eyelids open and gently stroke the sclera and cornea with a wisp of cotton or sterile gauze. Both eyes should blink in response to this stimulus. Dropping normal saline onto the sclera is an alternative to cotton or gauze that will reduce the chance of abrasion. Test the blink reflex in each eye in sequence, observing both the response in the ipsilateral and contralateral eye. The following are the important blink reflex patterns found in comatose patients (Fig. 2.3):

1. Normal responses in both eyes indicate preserved integrity of the blink reflex pathways in the pons and medulla (Fig. 2.3a).
2. Stimulation of the right eye produces no blink in either eye, while stimulation of the left eye produces normal blink responses in both eyes (Fig. 2.3b). This pattern points to dysfunction of the right trigeminal nerve or sensory nuclei in the pons and medulla.
3. Stimulation of either eye fails to produce a blink response in the right eye (Fig. 2.3c). The lesion in this case is in the right facial nucleus or nerve.
4. Stimulation of either eye produces a blink in the ipsilateral eye, but not in the contralateral eye (Fig. 2.3d). This pattern suggests disruption of the pathways connecting the trigeminal nuclei to the contralateral facial nucleus in the pons and medulla.
5. Bilaterally absent blink responses (Fig. 2.3e). This points to severe brainstem dysfunction, which may be due to structural or metabolic processes. Patients who wear contact lenses may also lose corneal sensitivity and, therefore, their blink responses.

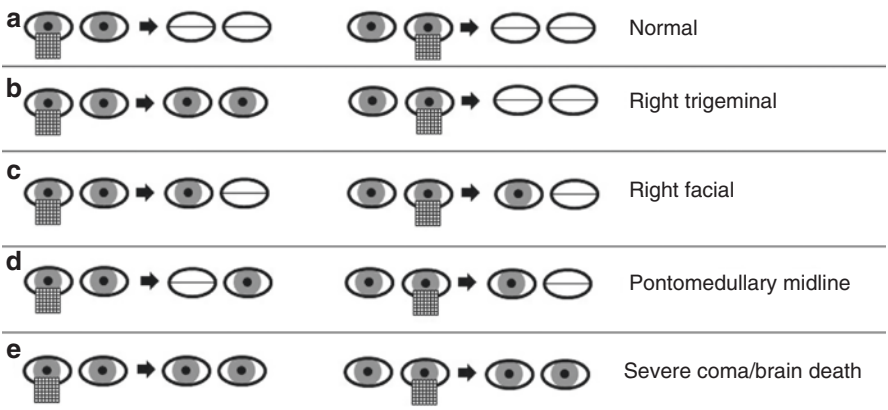

Fig. 2.3 Common patterns of blink reflex testing in patients in coma. See text for details

Eye Position

Horizontal Eye Position

The frontal eye fields (FEF) in the frontal lobes are the most important structures in the supranuclear control of horizontal eye movements. Projections from the FEF synapse with the contralateral abducens nucleus. Thus, activation of the right FEF or left abducens nucleus produces leftward eye deviation. Supranuclear, nuclear, and infranuclear lesions may lead to abnormal eye positions which can help to localize the process responsible for coma. In all cases, it is helpful to interpret eye deviation with respect to a hemiparesis, if present (Fig. 2.4):

1. Destructive right frontal lesions such as strokes or tumors produce rightward deviation of the eyes accompanied by left hemiparesis (Fig. 2.4a).
2. Irritative right frontal lesions such as seizures produce leftward deviation of the eyes. There may or may not be a left hemiparesis (Fig. 2.4b).
3. Right thalamic lesions (particularly hemorrhages, which may irritate the thalamic intralaminar nuclei) produce "wrong-way eyes" which are deviated to the left and are accompanied by left hemiparesis (Fig. 2.4c) [2].
4. Right pontine lesions produce leftward eye deviation. Left hemiparesis may or may not be present (Fig. 2.4d).

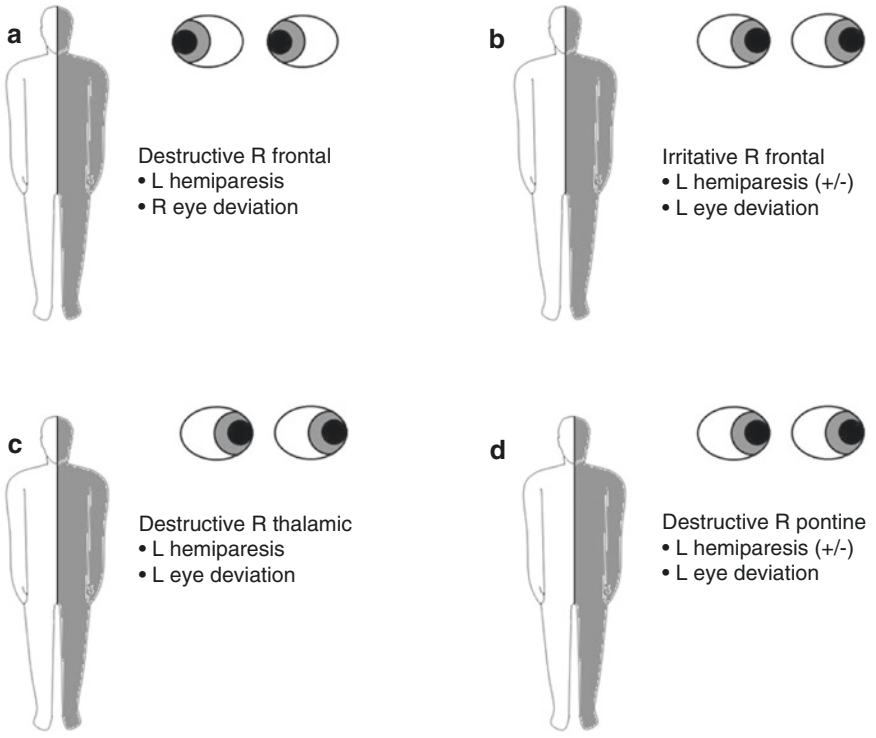

Fig. 2.4 Patterns of horizontal eye deviation and hemiparesis in patients with coma

Horizontal *dysconjugate* (the eyes look in different directions) gaze abnormalities are often helpful in localizing coma. Common patterns include:

1. Exodeviation (outward deviation) of both eyes. This is the pattern seen in many patients with coma and usually does not have localizing value.
2. Hypo- and exodeviation of one eye ("down and out") secondary to third nerve palsy.
3. Esodeviation (inward deviation) of one eye secondary to sixth nerve palsy or increased intracranial pressure.

Vertical Eye Position

The supranuclear control of vertical eye movements is more complex and involves the bilateral frontal lobes and structures within the brainstem including the vestibular nuclei and interstitial nucleus of Cajal in the midbrain. The important abnormalities of vertical ocular eye position in coma include:

1. Downward deviation of the eyes ("the setting sun sign") suggesting a severe dorsal midbrain lesion [3].
2. Vertical ocular misalignment pointing to skew deviation from a brainstem lesion or fourth nerve palsy.
3. Hypo- and exodeviation of one eye ("down and out") secondary to third nerve palsy.

Spontaneous Eye Movements

The spontaneous eye movements of comatose patients are usually slow and roving or absent altogether. Absent eye movements suggest a greater depth of coma, and, possibly, brain death, but do not have particular localizing value. Ocular bobbing is characterized by quick downward eye movements which are followed by a slower return back to the primary position and classically reflect pontine damage [4]. Dipping refers to slow downward eye movements with a quicker upward return. Bobbing and dipping may also have inverse forms, in which the first movement is upwards rather than downwards.

Vestibulo-Ocular Reflex

The vestibulo-ocular reflex is assessed in comatose patients by the head thrust maneuver or by cold caloric testing. To perform the head thrust maneuver, grasp the head by the forehead and chin. Peel the eyelids open and turn the head briskly to one side. The eyes will turn in the direction opposite of head rotation in patients with intact brainstem function. Dysconjugate eye movements may accompany structural brainstem lesions. Eye movements will be absent in patients who are deeply comatose or brain dead. Do not use the head thrust maneuver in patients with possible

cervical spine instability, as neck manipulation may worsen motor deficits and even lead to paralysis.

Because the head thrust maneuver is only a weak stimulus to eye movement, many comatose patients require cold caloric testing to activate the vestibulo-ocular reflex. To test cold caloric responses, place the head of the bed at 30° above the horizontal, thereby aligning the horizontal semicircular canal parallel to the ground. Examine the auditory canal to ensure that excessive cerumen accumulation will not interfere with the test and disimpact the ears as necessary. Fill a 60-mL syringe with ice water and attach the syringe to a short piece of intravenous tubing. Place the tubing into the ear and infuse the ice water slowly over 5 minutes. If brainstem function is intact, then the eyes should deviate towards the side of the ice water infusion. After performing the test on one ear, wait approximately 5 minutes for the vestibular system to reset, and test the opposite ear. Important patterns of abnormal oculocephalic response testing are shown in Fig. 2.5:

1. Cold water placed in either ear produces ipsilateral eye deviation of both eyes (Fig. 2.5a). This is the expected response in a patient with a metabolic encephalopathy and an intact brainstem.
2. Cold water placed in the right ear produces no response; cold water placed in the left ear produces tonic ipsilateral eye deviation (Fig. 2.5b). This is the pattern seen in patients with right vestibular nerve or lateral pontine damage.

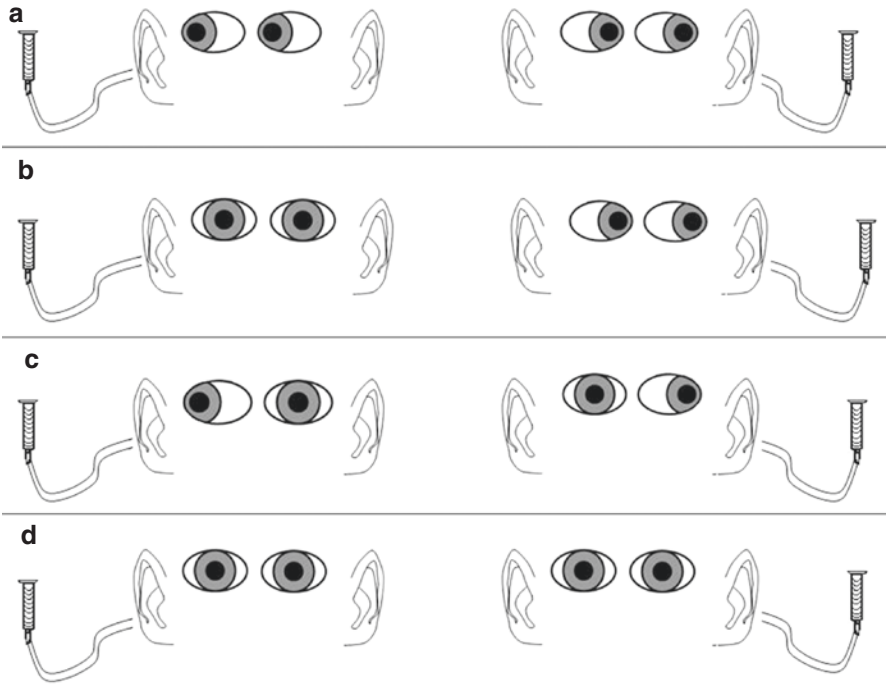

Fig. 2.5 Important patterns of cold caloric testing in patients with coma

3. Cold water placed in the right ear produces rightward eye deviation of the right eye only; cold water placed in the left ear produces leftward eye deviation of the left eye only (Fig. 2.5c). This is consistent with a midline lesion of the midbrain and pons producing bilateral internuclear ophthalmoplegia (Chap. 6).
4. Cold water placed in either ear produces no response (Fig. 2.5d). This occurs with severe coma or brain death.

Motor Examination

The motor examination helps to determine the presence and severity of coma and in some cases localizes the responsible lesion. Movements may be divided into the following four categories:

Spontaneous and Purposeful

Spontaneous, purposeful movements indicate that the patient is not comatose and should prompt evaluation for encephalopathy as detailed in Chap. 1.

Spontaneous but Nonpurposeful

For comatose patients, the most important spontaneous, nonpurposeful movement is polymyoclonus caused by anoxic brain injury and characterized by brief muscle jerks followed by relaxation of the arms, legs, and face. Sometimes polymyoclonus may take the form of violent jaw closure and result in tongue laceration or even severing of a mechanical airway (Chap. 14).

Reflexive

Comatose patients may demonstrate one of several reflex movements. In most patients, these are limited, local, nonpurposeful movements. They may be differentiated from normal movements by their lack of habituation to repeatedly applied, painful stimuli. The most widely known reflex movements in coma are decorticate and decerebrate posturing. In decorticate posturing, a painful stimulus causes flexion at the elbows, wrists, and fingers and adduction of the arms. In decerebrate posturing, a painful stimulus causes internal rotation of the arms with extension at the elbows and flexion-pronation at the wrists. In both decorticate and decerebrate posturing, there is extension at the hips, extension at the knees, and plantarflexion at the ankles. Classically, decorticate lesions arise from lesions superior to the red nucleus in the midbrain, while decerebrate lesions arise from lesions inferior to the red nucleus and superior to the vestibular nuclei in the medulla. The anatomic basis of decorticate and decerebrate posturing is less well defined in humans than in laboratory animals, though, and both may result from nonstructural, metabolic processes or from brainstem pathology. When caused by structural lesions, both forms of posturing are associated with a poor outcome, with decerebrate posturing portending a worse prognosis.

Absent

If the patient does not move spontaneously or in response to verbal command, compress the fingernail or toenail bed with the handle of a reflex hammer. Severely

encephalopathic patients but not those in coma may move the hand or foot away from such a stimulus with purpose. In some patients, a painful stimulus may produce only a facial grimace or heart rate elevation with no visible motor response in the limbs. This lack of a motor response in the presence of a preserved autonomic response is due either to severe brain damage or to neuromuscular dysfunction (Chap. 12). Absent movements with no change in heart rate suggests severe coma or brain death.

Respiratory Patterns

Abnormal respiratory patterns may suggest specific anatomic localizations of coma [1]. The classic patterns are often not observed, while the patient is intubated, sedated, and paralyzed but may become obvious if mechanical ventilation is discontinued temporarily. Cheyne-Stokes breathing is characterized by hyperpneic phases which build to a crescendo and then taper to apneic periods lasting for 10–20 seconds. This pattern is common in congestive heart failure and usually indicates intact brainstem function. Hyperventilation is associated with toxic and metabolic encephalopathies, generally those which produce metabolic acidosis. Central neurogenic hyperventilation is rare and is usually seen in the context of infiltrating brainstem glioma or lymphoma [5]. Apneustic breathing is characterized by 2- or 3-second pauses that occur at the end of inspiration and expiration and reflects pontine damage. Ataxic breathing has an irregular, gasping quality and is secondary to lower pontine or upper medullary dysfunction.

Investigation of Impaired Consciousness and Coma

Approximately 2/3 of coma is due to medical conditions, such as metabolic abnormalities and toxins, while the remaining 1/3 is due to structural causes such as trauma, brain hemorrhage, or tumor [1]. Because the number of potential causes of coma is quite large, it is helpful to divide the investigation into three phases based on the frequency of the responsible causes and the ease of obtaining diagnostic testing:

Phase 1: History, Examination, and Basic Studies

By the time a neurologist is consulted, a basic metabolic workup and CT scan of the brain are usually available. This information helps to establish one of the following diagnoses:

- Trauma – Patients with head trauma sufficient to cause coma almost always have abnormal head CT scans. In addition to skull fractures, abnormalities following trauma include epidural, subdural, intraparenchymal, and subarachnoid hemorrhages. Some patients have no clear evidence of fracture or hemorrhage, but CT shows evidence of diffuse axonal injury.

Table 2.1 Medical causes of coma

Hypoglycemia
Hyperglycemia
Renal failure
Hyponatremia
Hypernatremia
Hepatic failure
Hypothyroidism
Hyperthyroidism
Hypercalcemia
Systemic infection
Intoxication with:
Alcohol
Cocaine
Barbiturates
Opioids
Benzodiazepines
Amphetamines
Acetaminophen

- Intracranial mass lesion – Bilateral frontal or brainstem lesions including tumors, abscesses, and intracranial hemorrhages may all lead to coma.
- Subarachnoid hemorrhage – Aneurysmal rupture leading to subarachnoid hemorrhage is an important cause of coma that may be detected with CT scan (Chap. 19).
- Hypoxic-ischemic injury – Whether due to anoxia following cardiac arrest or to severe hypoxia secondary to pulmonary disease, irreversible brain damage occurs after minutes of global ischemia and is among the most serious causes of coma.
- Toxic or metabolic disturbances with normal imaging studies – Comatose patients with normal CT scans usually have a toxic or metabolic disturbance, often more than one. Routine laboratory testing is generally sensitive to the conditions listed in Table 2.1.

Phase 2: MRI, EEG, and Lumbar Puncture

Although history, CT scan, and basic laboratory studies often disclose the etiology of coma, further evaluation is necessary should these initial investigations fail to identify the responsible process.

MRI serves several purposes in patients with coma of unclear etiology. Diffusion-weighted MRI identifies hypoxic-ischemic changes several days before they are detectable by routine head CT. MRI may also disclose two specific infarctions that are poorly visualized by CT. The first is infarction in the paramedian thalamic artery, which supplies the intralaminar nuclei of the thalamus and rostral midbrain (Fig. 2.6) [6]. The second is infarction of the base of the pons leading to the locked-in state. Other causes of coma which may be missed by CT but detected by MRI include occult encephalitis or posterior reversible encephalopathy syndrome (Chap. 1).

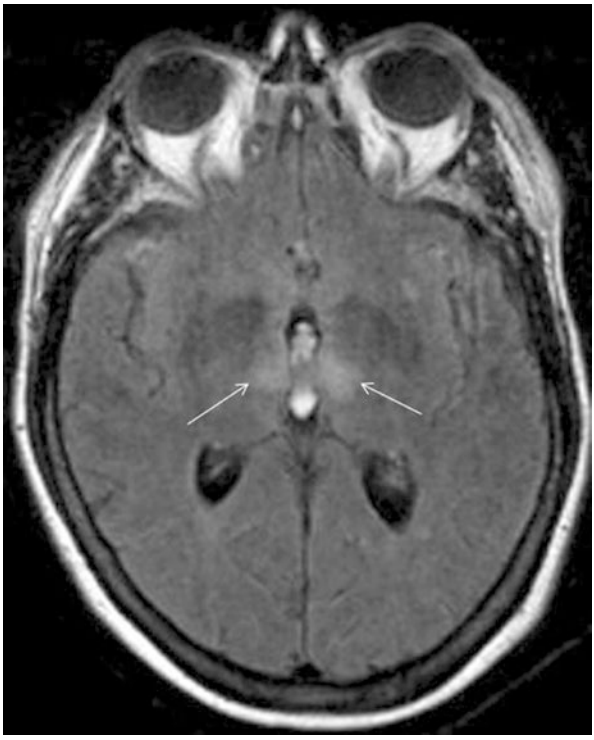

Fig. 2.6 Axial FLAIR MRI in a patient with paramedian thalamic artery infarction. This is an uncommon cause of coma, but it is important to recognize because it is easy to overlook. The bilateral thalamic hyperintensities are quite symmetric, and may be misdiagnosed as artifact

EEG helps to establish the presence of severe encephalopathy or brain death in unclear cases of coma. A more important application of EEG in comatose patients, however, lies in its ability to detect nonconvulsive status epilepticus (NCSE), a potentially reversible condition which often eludes clinical diagnosis (Chaps. 1 and 20). Continuous rather than routine (30-minute) EEG should be employed if NCSE is suspected, as 20% of patients may have their first seizures only after more than 24 hours of monitoring [7].

Lumbar puncture should be performed to evaluate for central nervous system infections, particularly bacterial meningitis and herpes encephalitis (Chap. 1).

Phase 3: Uncommon Etiologies and Coma Mimics

If the diagnosis remains unclear after an initial panel of investigations, MRI, EEG, and lumbar puncture, then consider less common toxins, neuromuscular mimics of coma, and psychogenic unresponsiveness.

Some toxins that may not be detected by routine toxicology screens are listed in Table 2.2. Consultation with a toxicologist is often helpful when considering these less common agents.

Severe neuromuscular disorders may lead to a state of profound weakness that mimics coma. Conditions such as Guillain-Barre syndrome, myasthenia gravis, and

Table 2.2 Less common toxins which lead to coma

Rohypnol
Ketamine
Phencyclidine
Ethylene glycol
Methanol
Antidepressants
Anticholinergics
Anticonvulsants

botulism are usually diagnosed before weakness mimics coma, but occasionally motor function declines so precipitously that the deterioration may go unrecognized. Critical illness neuromyopathy may also be severe to the point that it mimics coma. Rapidly progressive weakness and difficulty weaning from the ventilator due to neuromuscular disease acquired in the intensive care unit are discussed further in Chap. 12.

Psychogenic unresponsiveness secondary to conversion disorder, malingering, or catatonia may be profound to the point that it mimics a comatose state. Obviously, exhaustive medical evaluation must be conducted before these possibilities are even considered: review all imaging studies, EEG, lumbar puncture, blood tests, and toxicology screens. For patients with conversion disorders or malingering, cold caloric testing may cinch the diagnosis and cure the coma by inciting violent nausea and vomiting. Although patients with psychiatric disorders do not have an organic explanation for coma, they require attention and life support that is just as careful as that which is provided to patients with organic neurologic disorders.

Prognostication in Coma

The ability to accurately predict the outcome of a comatose patient is essential, as it provides families with reasonable expectations about the potential for recovery and advisability of continuing life support. Prognostication is based on the proximate cause of coma, the neurologic examination, and, in some instances, diagnostic test results.

Prognosis of patients with coma due to cardiac arrest is the most widely studied. Often, the goal in cardiac arrest patients is to define patients who have no chance of a good neurologic outcome, allowing decisions about withdrawal of aggressive care. If any reasonable chance of a good outcome remains, aggressive supportive care must be continued. The following examination and laboratory results predict against a meaningful neurological recovery in patients who have sustained a cardiac arrest and *should be applied only to patients with this specific etiology*. Take note that persistent hypothermia and pharmacologic sedation must be excluded as alternate causes of coma [8–10]:

- Absence of brainstem reflexes at any time
- Somatosensory evoked potentials showing absent N20 responses at days 1–3
- Neuron-specific enolase level >33 μg/L
- Absent pupil or corneal response at day 3
- Extensor posturing or absent motor response at day 3

These criteria may be applied to patients treated with hypothermia after cardiac arrest with two modifications. First, elevated neuron-specific enolase and motor response criteria are not of sufficient specificity to predict a poor prognosis in this population [10]. Second, authoritative statement about coma prognosis should wait until at least 72 hours after cardiac arrest and rewarming. Unless supplemental tests are available, be cautious about providing too much prognostic information before this time point and continue to provide maximal supportive care.

Although post-arrest seizures, particularly status epilepticus and myoclonic seizures, are a poor prognostic sign, they do not carry the same predictive value as the examination and laboratory findings described above [11].

The Persistent Vegetative State

After several days to a few weeks of deep coma, patients may appear to awaken and enter a vegetative state, which is given the name persistent vegetative state (PVS) if it lasts for at least 1 month [12]. This state is characterized by roving or tracking eye movements and what appears to be an irregular sleep-wake cycle. These patients, however, do not interact with their environment in a meaningful way. They may grunt or moan but do not speak or comprehend. PVS is the result of bilateral cortical damage with relatively preserved diencephalic and brainstem function. Although it may seem that PVS is a better cognitive state than coma, its ultimate prognosis is still quite poor: at 1 year following onset, only 1% of non-traumatic and 7% of traumatic PVS patients had a good outcome [13]. PVS should be considered permanent if it persists for 3 months in patients with non-traumatic conditions and for 12 months in patients with traumatic brain injuries [14]. News stories of patients recovering after years of coma or PVS are exceptional and should not be used to give families false hope.

The Minimally Conscious State

Patients recovering from coma or a vegetative state, particularly those due to traumatic etiologies, may enter a minimally conscious state (MCS) that resembles PVS with several important differences. Patients are able to respond to external stimuli in a limited way by nodding their head yes or no, verbalizing in a very basic fashion, holding objects appropriately, and following simple commands [15]. While recovery to functional independence remains unlikely in MCS, the neurologic ceiling is higher than it is for PVS [16]. Anecdotal reports and small case series have shown improvement in MCS patients treated with zolpidem, amantadine, levodopa, or transcranial magnetic stimulation [17].

Brain Death

Brain death is defined as the complete loss of brain function despite preserved cardiac function. It is particularly important to recognize brain death in order to allow decisions about withdrawing aggressive medical support and to plan for organ

procurement. Before a patient is diagnosed with brain death, all potentially reversible causes of coma must be corrected. Sedatives such as midazolam and propofol must be discontinued, and core temperature should be raised to at least 97 °F. Next, the patient must be carefully examined, often using an institution-specific brain death protocol. A patient who is brain dead must be unarousable to any stimulus, lack pupillary and corneal reflexes, have no cold caloric responses, and not gag or cough when suctioned. Deep tendon reflexes may be (and often are) preserved. Many institutions require re-examination several hours or a day later, though this repetition is unlikely to alter the clinical impression of brain death: in one study, a second examination reversed the diagnosis in 0 of more than 1200 patients [18].

The apnea test is used to confirm brain death. Hypercarbia is a profound stimulus to breathe, and when it fails to produce a respiratory effort, there is severe brain damage incompatible with life. Before performing the apnea test, obtain a baseline arterial blood gas sample and note the partial pressure of carbon dioxide (P_{CO2}). Next, preoxygenate the patient with 100% oxygen for at least 10 minutes. Following preoxygenation, discontinue mechanical ventilation while continuing to provide oxygen via a face mask. The apnea test is positive if no respiratory efforts are visible after 10 minutes of ventilator discontinuation. Before reconnecting the patient to the ventilator, draw a repeat arterial blood gas sample to confirm the adequacy of hypercarbia: the P_{CO2} level must reach an absolute level of 60 mm Hg or a relative level 20 mm Hg higher than the baseline level.

In some patients, difficulties with interpreting the neurological examination or minor metabolic abnormalities prevent airtight confirmation of brain death. In such cases, supplementary diagnostic tests establish brain death by showing absence of cerebral electrical activity or cerebral blood flow. These include:

- EEG showing electrocerebral silence
- Somatosensory evoked potentials showing absent N20 responses
- Absent cerebral blood flow as determined by:
  - Transcranial Doppler ultrasound
  - Cerebral angiography
  - Nuclear scanning

Increased Intracranial Pressure

Expansion of intracranial contents is limited by the rigid confines of the skull. Blood, tumor, abscess, and edema are tolerated to a limited extent before symptoms and signs of increased intracranial pressure develop. In its earliest stage, increased intracranial pressure causes nonspecific headaches and visual blurring. Recognition of increased intracranial pressure at this stage may allow the responsible process to be diagnosed and reversed, thereby preventing additional neurologic deterioration. Funduscopic examination may show papilledema (Chap. 19, Fig. 19.2). Further increases in intracranial pressure lead to encephalopathy, seizures, and a variety of focal neurological findings. The most devastating consequences of increased

intracranial pressure are the herniation syndromes in which brain tissues are displaced from their normal locations, compressing or damaging otherwise healthy structures. The most important of these syndromes are uncal and transtentorial herniation.

Uncal Herniation

A hemispheric mass or edema may cause expansion of one cerebral hemisphere relative to the other, leading to herniation of the uncus of the ipsilateral temporal lobe medially and inferiorly into the tentorial notch [1]. The earliest signs of uncal herniation are ipsilateral pupillary dilatation produced by stretching or compression of the third nerve and a decrease in consciousness produced by compression of the upper brainstem. Pupillary dilatation in the presence of preserved consciousness, however, is never due to uncal herniation [1]. As uncal herniation progresses, hemiparesis usually develops *ipsilateral* to the herniating mass as the *contralateral* cerebral peduncle is compressed, the so-called Kernohan notch phenomenon. Less commonly, the ipsilateral cerebral peduncle is compressed leading to a contralateral hemiparesis. Thus, pupillary dilatation is more reliable than hemiparesis in lateralizing uncal herniation. Shearing or compression of the posterior cerebral arteries in the tentorial notch may lead to strokes and cortical blindness. Because uncal herniation may progress rapidly to a state of irreversible neurologic compromise or death, it must be identified as quickly as possible to allow treatment of the responsible source.

Transtentorial Herniation

An expanding midline lesion may cause herniation downwards through the tentorium, compressing the thalamus and brainstem [1]. In early transtentorial herniation, the patient appears to be sleepy with small, minimally reactive pupils. It is very easy to misdiagnose the patient with a metabolic encephalopathy, and a high index of suspicion must be maintained in order to make the diagnosis at this stage, as further progression is generally associated with a poor outcome. As herniation continues, the midbrain is compressed, leading to paresis of upgaze, unresponsiveness, and decorticate posturing. Continued downward herniation compromises the pons, resulting in loss of lateral eye movements and decerebrate posturing or motor unresponsiveness. In the final stage of transtentorial herniation, medullary compression produces irregular breathing, flaccidity, and eventually death.

Other Herniation Syndromes

Subfalcine herniation is caused by a hemispheric mass causing medial displacement of ipsilateral cerebral contents inferior to the falx cerebri. Upward herniation occurs

when a large cerebellar mass, infarct, or hemorrhage leads to expansion of the posterior fossa contents superiorly. Tonsillar herniation involves herniation of posterior fossa contents inferiorly with compression of the medulla or cervicomedullary junction by the cerebellar tonsils. Extracranial herniation is displacement of intracranial contents externally through a traumatic or iatrogenic skull defect.

Management of Increased Intracranial Pressure

The definitive treatment of increased intracranial pressure is removing the proximate cause, whether it is hemorrhage, edema, tumor, or abscess (see also Chaps. 21 and 23). In many cases, this is not practical, and medical management becomes the focus of treatment.

Once neurological deterioration due to increased intracranial pressure is identified, the first step is to improve cerebral venous drainage by placing the head of the patient's bed at a 45° angle. Next, intubate the patient and hyperventilate them to a carbon dioxide partial pressure (P_{CO2}) of 26–30 mm H_2O. This decrease in P_{CO2} produces an alkalotic cerebral vasoconstriction and increases the volume available to the brain parenchyma. Reduction of the P_{CO2} to 25 mm H_2O or lower increases the risk for cerebral ischemia and should be avoided. The benefits of hyperventilation usually last for only a few hours, and sustained hyperventilation may increase the chance of cerebral ischemia. Sedation with propofol or fentanyl will prevent the patient from fighting the ventilator and reduce the chance of a gag or cough leading to a dangerous spike in intracranial pressure.

Placement of an intracranial pressure monitoring device can be considered for patients in whom the neurologic examination cannot be monitored reliably. Studies of the relationship between intracranial pressure monitoring on survival have created considerable controversy, however, and the benefit on tailoring treatments to intracranial pressure readings is not clear [19]. For most patients, the goal is to avoid sustained intracranial pressure of >20 mm Hg. In patients without invasive intracranial pressure monitoring, frequent serial examinations and a daily head CT to look for progressive midline shift should be performed.

Osmotic diuretics are the mainstay of medical management of increased intracranial pressure. The two main treatment options are mannitol and hypertonic saline, and each has its advocates. The osmotic diuretic mannitol is initially administered as an intravenous bolus of 1 g/kg followed by smaller boluses of 0.25–0.5 g/kg every 6 hours, as dictated by clinical response and intracranial pressure readings, if available. The serum osmolality should be measured with each dose of mannitol and be kept below 320 mOsm. Hypertonic saline is administered as a 30 mL bolus of a 23.4% solution or a 150 mL bolus of 3% solution, with a maintenance infusion of 3% solution to keep the serum sodium concentration between 145 and 150 mEq/L, again monitoring for clinical response or reduction in intracranial pressure readings.

In patients in whom the source of increased intracranial pressure cannot be addressed, consider craniotomy and temporal lobectomy to reduce rapidly increasing intracranial pressure. Because most patients who reach the stage at which this intervention is considered have a poor prognosis, decisions about neurosurgical intervention should be made very carefully. Other treatments including barbiturates, corticosteroids, and therapeutic hypothermia do not improve outcome in patients with increased intracranial pressure and should be avoided.

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Aphasia

3

Introduction

Aphasia is an acquired disorder of language resulting from brain damage. Understanding the history, controversies, and neuropsychology of aphasia are requirements for every neurologist in training, and there are several excellent reviews available which discuss these topics in greater detail [1–3]. For bedside purposes, however, a clinically focused approach consisting of the following three steps will suffice:

1. Determine if the problem is aphasia or a mimic.
2. Classify the type of aphasia based on examination.
3. Determine the etiology and attempt to treat it if possible.

Bedside Examination of the Aphasic Patient

Because the most common acute cause of aphasia is ischemic stroke, it is important to evaluate the patient rapidly in order to determine their eligibility for intravenous thrombolysis. Once the patient is stabilized and decisions about acute stroke treatment have been made, you can assess language in greater detail. More than an academic exercise, the classification of aphasia helps to define the patient's present language capabilities and to predict their future ones. Correct classification of aphasia also allows succinct communication with other healthcare providers. For a neurologist's purposes, assessment of aphasia involves examining:

1. Spontaneous speech
2. Comprehension ability
3. Repetition
4. Confrontation naming
5. Reading, both aloud and for comprehension
6. Writing

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Spontaneous Speech

Careful listening to spontaneous speech while taking the history provides many of the essential details about a patient's language dysfunction.

Fluent speech is characterized by a normal or increased rate of word production with normal phrase lengths, while nonfluent speech is characterized by a paucity of verbal output and short phrase lengths. Fluent aphasics use excessive numbers of "filler" words such as prepositions and conjunctions. Despite the excessive number of words, content is lacking. Nonfluent aphasics generally use a preponderance of content-rich words such as nouns and verbs. While their utterances are short and agrammatic, they often convey a great deal of meaning. As a general rule, fluent aphasias are caused by language-dominant hemisphere lesions posterior to the central sulcus, while nonfluent aphasias are caused by dominant hemisphere lesions anterior to the central sulcus.

Paraphasic errors are word substitutions and may be classified broadly into semantic and phonemic errors. Semantic paraphasic errors are those in which the word produced is related in meaning to the target word. Examples of common semantic paraphasic errors include simplifications (e.g., *finger* for *thumb*), substitutions of one item for another of the same class (e.g., *toe* for *thumb*), and substitutions of the whole for the part (e.g., *hand* for *thumb*). Phonemic paraphasic errors are those in which inappropriate phonemes (sound segments) are substituted (e.g., *tadle* for *table*), omitted (e.g., *tale* for *table*), or added (e.g., *tadable* for *table*).

Articulatory errors are apparent word substitutions produced by patients with dysarthria. These are not technically paraphasias but in some cases may resemble phonemic errors.

Neologisms are new words formed from appropriate phonemes which do not resemble an identifiable target word. These are particularly characteristic of posterior aphasias such as Wernicke aphasia.

Comprehension

While it is generally true that patients with nonfluent aphasias comprehend spoken language better than those with fluent aphasias do, all aphasic patients have some degree of comprehension impairment. Conversely, the comprehension abilities of fluent aphasics (in whom comprehension is traditionally described as being poor) are usually preserved to some degree. When assessing comprehension, it is important to establish a floor and a ceiling of performance. In sequence, ask the patient to do the following:

- Follow commands which involve the midline of the body, such as opening and closing the eyes and sticking out the tongue. The ability to follow these commands is preserved in patients with all but the most severe aphasias.
- Perform simple limb movements such as raising the left or right hand or pointing to objects around the room. Keep in mind that right arm weakness and apraxia (Chap. 4) may accompany aphasia and impede the performance and interpretation of this type of test.

- Answer simple yes/no questions that require only head nodding. Be sure to alternate questions that elicit both yes and no responses, as many patients may continue to nod "yes" without actually understanding the questions.
- Follow in-sequence commands such as "point to the door, then the light, then the window."
- Follow multistep, disrupted-sequence commands such as "after pointing to the door, but before pointing to the light, point to the window." These are challenging, especially for nonfluent aphasics in whom understanding complex syntactic structures is impaired.
- Answer listening comprehension questions such as, "The wolf was chased and eaten by the sheep. Who died?" Questions such as this one, in which both the traditional subject-verb-object syntax and the expected logic of the sentence are altered, are often helpful in detecting subtle deficits in nonfluent aphasic patients with apparently preserved comprehension.

Repetition

While the ability to repeat is seldom applied to everyday life situations, testing repetition is useful in distinguishing among the different aphasia syndromes. The general rule is that repetition is poor in perisylvian aphasias but relatively preserved in extrasylvian aphasias. To test repetition, start with common, single-syllable words such as "cat" and "dog." The ability to repeat these words is preserved in all aphasics except those with the most severe difficulties. Next, test the ability to repeat simple subject-verb-object sentences such as, "The boy threw the ball." Finally, ask the patient to repeat complex sequences such as, "After coming home from work, they ate breakfast in the living room." Take note of the specific types of problems with repetition, if present. Patients with nonfluent aphasias tend to omit prepositions and conjunctions but repeat content-rich words correctly. Inattentive patients might be able to repeat only the first few (or last few) words of a complex phrase correctly. All repetition impairments should be judged in terms of their relative severity compared to other language deficits. For example, patients with transcortical motor aphasia may make some errors when attempting to repeat, but these errors are minor compared to their near complete absence of spontaneous speech.

Confrontation Naming

Some patients with aphasia have few deficits beyond word-finding difficulties and problems with confrontation naming, so-called anomic aphasia. A commonly used bedside method to test confrontation naming is to ask the patient to name your hand, finger, thumb, knuckle, and cuticle in sequence. This is a rough screen for anomia for high-, medium-, and low-frequency items. Aids such as the Boston Naming Test allow better quantification of naming deficits. Be cautious not to assign too much weight to mild anomia when using such an instrument, as impairments are common in older and less educated patients.

Reading

Reading deficits generally mirror spoken language deficits. Test for the ability to read individual words, short sentences, and brief passages of 100–200 words aloud. Look for both the ability to correctly pronounce individual words, maintain normal rhythms, and understand content.

Writing

Like reading, writing performance usually mirrors spoken language. Patients with nonfluent aphasias write short, agrammatic sentences full of content words, while those with fluent aphasias write long, often incomprehensible sentences with many paraphasic errors.

Aphasia Syndromes

While the following descriptions of the classical aphasia syndromes are clinically useful, they have several important limitations. First, they are largely described in patients with ischemic strokes in specific vascular territories. Many patients with aphasia secondary to trauma, tumor, or hemorrhage do not conform to these patterns. Second, there are numerous exceptions to even the most basic rules such as left-sided lesions cause aphasia in right-handed people, posterior lesions produce fluent aphasias, and extrasylvian aphasias do not affect repetition. Finally, aphasia may undergo a semiologic transformation over time. For example, a patient with global aphasia at initial presentation may transform to Wernicke aphasia several days later.

Broca Aphasia

Broca aphasia is characterized by nonfluent speech, relatively preserved comprehension, and impaired repetition. In its classical form, spontaneous output is limited to content-rich phrases of one or two words that are produced with great effort and poor melodic intonation. While patients understand simple sentences and can follow commands, longer, syntactically complex sentences reveal important comprehension limitations. Patients may be able to repeat single words, but longer phrases prove more challenging. Accompanying deficits include contralateral arm and face weakness. Broca aphasia is traditionally due to infarction of the frontal operculum and subcortical white matter (Fig. 3.1), although many patients with lesions isolated to these areas have partial syndromes rather than full-blown Broca aphasia [4].

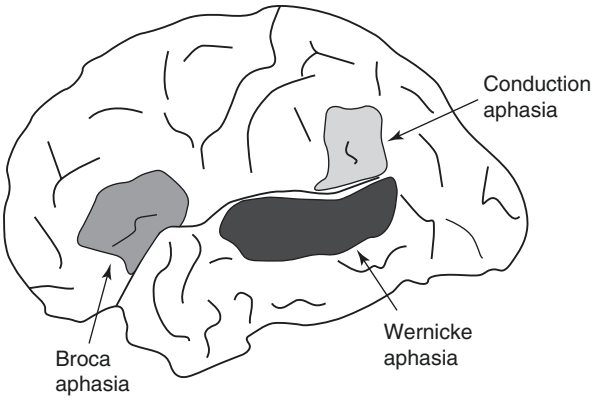

Fig. 3.1 Left lateral view of the brain demonstrating the rough localizations of the classical cortical aphasias

Wernicke Aphasia

Patients with Wernicke aphasia have fluent speech, often with an increase in the rate and quantity of verbal output to the point where it can be labeled as pressured. Content is sparse, consisting of excessive semantic and phonemic paraphasic errors, adverbs, adjectives, and grammatical connectors. The prosody, or rhythm and inflection of verbal output, is normal. Comprehension of both spoken and written language is poor. Patients with Wernicke aphasia are unable to repeat in a reliable manner and, in many cases, are not even able to understand the request to repeat. Patients with Wernicke aphasia may be completely unaware or unconcerned by their deficits. Additional neurological deficits may include contralateral hemibody sensory abnormalities and right-sided visual field cuts. The lesion associated with Wernicke aphasia is in the left superior temporal gyrus (Fig. 3.1) and is often produced by an embolus to the inferior division of the left middle cerebral artery.

Global Aphasia

Global aphasia is most often caused by a large middle cerebral artery infarction. Output is nonfluent and agrammatic, and in some cases, the patient may be mute. Both comprehension and repetition are poor. Global aphasia is usually accompanied by a severe right hemiparesis and often by forced leftward eye deviation.

Transcortical Motor Aphasia (TCMA)

The most obvious feature of TCMA is poor speech initiation, which may result in utterances that are only one or two words in length. Comprehension is relatively preserved. The difference between spontaneous speech and repetition is quite striking: some patients with TCMA may be able to repeat long sentences almost

verbatim, while others have very little spontaneous speech but are able to repeat the examiner's questions (echolalia). The most common lesion location is in the frontal subcortical white matter anterolateral to the left lateral ventricle [5]. TCMA may be due to left anterior cerebral artery infarction, in which case it is accompanied by right foot weakness.

Conduction Aphasia

The most obvious feature of spontaneous speech in conduction aphasia is the excessive number of paraphasic errors, most often phonemic ones. Circumlocution is also quite striking and may take the form of *conduite d'approche* in which the patient makes successive paraphasic errors that more closely approximate the desired word before finally arriving at that target. Fluency is generally preserved, although it may be slightly reduced as the patient attempts to correct their paraphasic errors or search for the appropriate word. Comprehension is relatively normal, but repetition is very poor. Conduction aphasia may be associated with contralateral homonymous hemianopsia or inferior quadrantanopsia. Conduction aphasia is usually due to lesions of the left supramarginal gyrus, insula, or temporo-parietal white matter (Fig. 3.1).

Transcortical Sensory Aphasia and Mixed Transcortical Aphasia

These aphasias are uncommon in the acute setting. Transcortical sensory aphasia is characterized by fluent output rich in nonspecific words such as "that" or "things," poor comprehension, and relatively spared repetition. It is most common in Alzheimer disease and semantic dementia (Chap. 4). Patients with mixed transcortical aphasia show poor fluency and comprehension with relatively preserved repetition. It is uncommon and most often due to large frontal or anterior thalamic lesions [1].

Subcortical Aphasias

Subcortical lesions may produce a wide variety of aphasias which I will not discuss in detail. Deficits may resemble one of the classical aphasias or may be nonspecific and restricted to anomia. The two most commonly described lesion locations for subcortical aphasia are the thalamus and the striatum/internal capsule [6].

Anomic Aphasia

Essentially any left hemispheric lesion may produce anomia with otherwise preserved language. Anomia may be the presenting deficit of an acute aphasia, or it may be the long-term remnant of a resolving aphasia.

Mimics of Aphasia

An essential step in evaluating a patient with a possible acute language disturbance is to determine whether they are actually aphasic. The three problems that are most often misidentified as aphasia are dysarthria, confusion, and aphemia.

Dysarthria

Dysarthria is an abnormality in the mechanical production of speech (Chap. 8). It is most easily distinguished from aphasia by the absence of word-finding or comprehension difficulties. Patients with dysarthria tend to make more consistent errors: for example, a patient with dysarthria is just as likely to make an error in the production of a single word or syllable, whereas a patient with aphasia will tend to make more errors with longer utterances. Dysarthric patients make many more errors with consonants than they do with vowels, whereas aphasic patients make errors that are more evenly distributed between consonants and vowels. In most cases, dysarthria is secondary to intoxication with drugs (both prescription and illicit) or alcohol or to a metabolic disturbance such as hyponatremia or hypoglycemia. Dysarthria is seen frequently in stroke patients, though it usually accompanies other language or motor deficits; *isolated* dysarthria as a manifestation of stroke is rare [7].

Confusion

Differentiating confusion from aphasia is often challenging, but doing so is very important because the metabolic derangements that produce confusion are quite distinct from the vascular lesions that are most commonly responsible for aphasia. Although confusion is principally a disorder of attention, any cognitive domain, including language, may be affected (Chap. 1). Language examination of the confused patient will often show normal fluency, poor comprehension, and normal repetition, potentially leading to the erroneous impression that the patient has a transcortical sensory aphasia. Confused patients are most reliably distinguished from aphasic ones by the presence of widespread behavioral abnormalities outside of the language domain.

Aphemia

Aphemia is characterized by severe articulatory planning deficits that may mimic nonfluent aphasia [8]. In most cases, patients are mute at presentation. Unlike patients with nonfluent aphasias, comprehension and written language are preserved in aphemia. The capacity to write lengthy, well-constructed sentences that contrast markedly with the sparse spontaneous verbal output is often astounding. Aphemia is caused by lesions within the left hemisphere, including the Broca area, the

premotor cortex, the motor strip, and the insula. It is usually accompanied by right hemiparesis. As acute mutism resolves, speech is initially slow, effortful, and poorly articulated. Complete recovery may occur over several days to a few weeks. It is important to recognize aphemia, as it usually has a better prognosis than the nonfluent aphasia syndromes with which it is confused.

Determining the Cause and Treatment of Aphasia

Acute aphasia is most commonly due to ischemic or hemorrhage stroke. Other sources of acute aphasia include head trauma, intracranial masses, seizures, and the postictal state. In the acute setting, a comprehensive evaluation of language may need to wait, as the strokes which often produce acute aphasia require rapid assessment and intervention (Chap. 21).

Primary progressive aphasia is discussed in more detail in Chap. 4.

Recovery and Rehabilitation of Acute Aphasia

Most recovery from aphasia takes place within the first 3–6 months after symptom onset [9]. The traditional notion that recovery beyond 1 year is rare may not necessarily be true [10]. Predictors of better prognosis include smaller lesions, younger patient age, and left-handedness. Patients with traumatic lesions tend to have better outcomes than those with ischemic or hemorrhagic ones. Recovery is mediated by the cortex adjacent to the lesion, subcortical structures, and the contralateral hemisphere [11]. Both formal (with a speech therapist) and informal (reintegrating the patient back into everyday communication with family, friends, and coworkers) rehabilitation programs are beneficial and should be initiated as soon as possible [12].

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Dementia

4

History

Dementia is the chronic and progressive loss of memory and at least one other cognitive function (language, praxis, object knowledge, or executive function) which interferes with a person's ability to perform their activities of daily living [1]. Although the history is the most important means of establishing a diagnosis, most patients with dementia provide only a vague account of their cognitive deficits, often stating that nothing is wrong or focusing on a minor respiratory, gastrointestinal, or orthopedic complaint. The patient frequently lacks awareness of their deficits, and collateral history must be obtained from a family member or friend. Because this narrative history may also be vague and unhelpful, directed questioning about specific deficits is sometimes the only effective strategy to establish the exact nature of the problem.

Memory

Ask whether the patient repeats themselves or asks the same questions in the space of a few minutes, as this is often the first reliable indication of a memory problem. A demented patient misplaces their keys, eyeglasses, or wallet more frequently than would be expected of someone who was simply absentminded. Other memory problems include forgetting to purchase items from the grocery store, missing appointments, and getting lost. Memory problems may lead to difficulty with the finances, as the patient often forgets charges or receipts when balancing their checkbook or paying online bills. Although all dementias include at least a component of memory problems, these are particularly important in Alzheimer disease.

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Language

Word-finding difficulties are an early deficit in many dementias, especially Alzheimer disease and primary progressive aphasia. The patient seems to search for the proper word for an excessive amount of time or has a tendency to substitute less specific words such as "thing," "that," or "the place" for more precise ones. Episodes in which speech appears to be slurred or garbled are a feature of dementia with Lewy bodies.

Praxis

Praxis is the ability to perform skilled movements, and apraxia is an important feature of many dementias, especially corticobasal degeneration and Alzheimer disease. Early evidence for apraxia includes difficulty with operating computers, smartphones, and other relatively newer technologies. Planning and preparing meals become problematic. As dementia progresses and apraxia worsens, problems with simpler and simpler tasks such as eating and toileting develop.

Visuospatial Function

Visuospatial deficits include problems with getting lost, misidentifying faces, and driving or parking. These problems are characteristic of posterior cortical atrophy but may occur in other forms of dementia. Patients with more advanced dementia may have difficulties with dressing properly.

Behavioral Abnormalities

Behavioral abnormalities occur early in frontotemporal dementia. Socially inappropriate behaviors including lewd comments, aggression, and excessive risk taking are common. At the opposite end of the behavioral spectrum, abulia, in which patients lack energy and motivation, spending most of their time in bed or watching television, is also seen in frontotemporal dementia. Visual hallucinations are a core feature of dementia with Lewy bodies, though many patients may be hesitant to admit that these are occurring because they are worried that their report might lead to psychiatric hospitalization. To ease into inquiries about hallucinations, ask first about vivid dreams and then about seeing unusual things, and if the patient does not endorse either of these, ask specifically about hallucinations. Wandering and nocturnal agitation are features of many moderate or advanced dementias. Rapid eye movement (REM) sleep behavioral disorder is characterized by punching, kicking, or screaming out in the middle of sleep and may predate other symptoms of dementia with Lewy bodies and other synucleinopathies by many years.

Gait Difficulties

Although gait difficulties are common and somewhat nonspecific in the elderly (Chap. 18), they may point to specific causes of dementia including normal pressure hydrocephalus, vascular dementia, and progressive supranuclear palsy.

Relevant Medical History

Obtain a complete medical history in all patients who present with suspected dementia. A history of HIV infection, cardiac surgery, renal or hepatic failure, or hypothyroidism may point to explanations for cognitive decline other than one of the degenerative dementias. It is also helpful to screen briefly for sleep disorders, disabling pain, and depression. These medical problems often mimic dementia, and because they are reversible, it is important to identify and treat them as soon as possible. Medications, especially narcotics, benzodiazepines, and anticonvulsants, may produce reversible cognitive dysfunction. Seek a substance abuse history, as abuse of alcohol and illicit drugs may produce potentially reversible cognitive decline that mimics frontotemporal dementia.

Age of Onset and Tempo

The age of onset of dementia is often helpful in classifying it. While most demented patients are older than 65, frontotemporal dementia and early-onset Alzheimer disease may begin in patients in their 40s or 50s. Posterior cortical atrophy and logopenic progressive aphasia are Alzheimer disease variants that tend to occur in patients younger than those with the amnestic form of Alzheimer disease. Deficits in most dementias are acquired in a gradual fashion, but some are characterized by a subacutely progressive onset over a few weeks to months (Creutzfeldt-Jakob disease or Hashimoto encephalopathy), or a sudden and stepwise onset (vascular dementia). Patients with dementia with Lewy bodies may have fluctuating behaviors including daytime drowsiness and lethargy, naps lasting at least 2 hours, staring into space for long periods, and episodes of disorganized speech [2].

Examination

Mental Status Examination

The mental status examination begins informally as the history is being obtained. Make note of any word-finding difficulties, repetition of details, or vague answers. Patients with moderate-to-severe dementia may not be able to provide any relevant

history whatsoever. Observe for bizarre comments or general sluggishness suggestive of frontotemporal dementia, or bradykinesia or bradyphrenia indicative of dementia with Lewy bodies.

Keep in mind that poor performance on components of the mental status examination may represent the patient's cognitive baseline rather than an acquired problem. Before judging any deficiencies, inquire about the length of the patient's formal education, occupation, and level of intellectual engagement prior to the onset of cognitive decline.

Mental status testing is often time-consuming. In some cases, thorough cognitive assessment may require more detail than a single office visit allows, particularly in the early stages of dementia when the problems may be subtle or when the patient has a high premorbid level of function. The Mini-Mental Status Examination and Montreal Cognitive Assessment are good brief screening examinations, but do not accurately classify dementia or milder deficits in most cases [3]. The brief mental status examination summarized in Table 4.1 and described in detail in this chapter can be completed in 10 minutes and provides both a general picture of a patient's cognitive abilities and details about problems in specific cognitive domains.

Attention

A variety of bedside tests are available to assess attention (Chap. 1). After establishing basic orientation to person, place, and time, ask the patient to recite the months of the year backwards. Attention is relatively preserved until the intermediate-to-advanced stages of Alzheimer disease, while it may be affected earlier in the course of frontotemporal dementia.

Language

Chapter 3 provides more detailed instructions for the assessment of language. Additional tests that are important in patients with suspected dementia assess semantic and phonemic fluency.

Table 4.1 Summary of mental status examination

Orientation to person, place, and time
Months of the year backwards
Language testing for fluency, comprehension, and repetition (Chap. 3)
Semantic fluency
Phonemic fluency
Recall of four words at 5 minutes
Target cancellation (Chap. 1)
Praxis testing
House construction
Clock construction
Luria test
Stroop test
Anti-saccade test
Frontal release signs

Semantic Fluency

To test semantic fluency, ask the patient to name as many animals as they can in 1 minute. Highly detailed normative values stratified by age and educational level are available, but a healthy older person will be able to name roughly 12 different animals [4]. Early loss of semantic fluency compared to phonemic fluency suggests the possibility of Alzheimer disease or semantic dementia [5]. These patients may be able to name only four or five animals in 1 minute, often repeating more familiar animals several times during the course of the test or having a long gap after naming two or three animals at the beginning of the test.

Phonemic Fluency

To test phonemic fluency, ask the patient to generate a list of words, exclusive of proper nouns, beginning with the letter "F," "A," or "S." It may be helpful to perform this test several minutes after testing semantic fluency: many patients who perform the tests consecutively will restrict their responses to animals that begin with the target letters. Again, there are normative values stratified by age and educational level. A healthy older person should be able to name roughly ten FAS words in 1 minute [4]. Patients with dementia with Lewy bodies and frontotemporal dementia generally show more difficulty with this task when compared to animal list generation, while patients with Alzheimer disease do better on the FAS test than on the animal listing test [5].

Memory

Asking the patient to tell you about a few current events or sports stories is a good screening test for memory problems. If they cannot tell you anything spontaneously, try to trigger their memory by providing hints about an item in the news. If they still draw a blank, ask the patient to name the president, governor, or best player on the local baseball or football team. If they are not capable of doing even this last task, ask them if they know the date or season.

Verbal recall of a four-word list is a good test of episodic memory. Begin by telling the patient that you will ask them to recall four words in 5 minutes. When selecting target words, use both words that have physical manifestations such as "apple" and also conceptual ones to which visual tags cannot be so readily assigned, such as "wisdom." Present the word list at least three times and instruct the patient to repeat it back to you after each presentation. A patient who cannot repeat the word list has attentional problems that will prevent accurate assessment of their recall abilities. Complete the remainder of the mental status examination, and ask the patient to recall the four words after 5 minutes elapse. Older patients are generally able to recall three or four of the words and usually can select the fourth word from a multiple-choice list or recall it if you give them a hint about the category to which the item belongs. Patients with Alzheimer disease have problems not only with recalling the words but also with recognizing them from a list or guessing them from a category. In the very early stages of memory problems, a four-item list may not be sensitive enough to detect memory deficits, and more detailed neuropsychological evaluation may be required.

Praxis

Apraxia is defined as the inability to perform a learned movement in response to the stimulus which normally produces it. In order for the apraxia label to be appropriate, all elemental neurologic functions such as strength, sensation, language, and attention must be preserved. Apraxia was originally described by Liepmann, and his division of apraxia into ideomotor, ideational, and limb-kinetic forms largely persists to this day, despite substantial controversies. Interested readers are referred to Ochipa and Rothi's review on the topic, as I will discuss only ideomotor apraxia in a limited format here [6].

Ideomotor apraxia is characterized by errors in positioning, orientation, sequencing, and timing of limb movements. A simplified heuristic of the neuroanatomy of ideomotor apraxia is found in Fig. 4.1 [6]. Verbal, visual, or somatosensory inputs synapse with movement representations in the left inferior parietal lobule. These, in turn, activate motor programs in the supplementary motor area of the left frontal lobe. These motor programs activate movement of the right side of the body via connections with the motor cortex of the left hemisphere. They also cross to the motor cortex of the right hemisphere via the corpus callosum, thereby activating movements of the left side of the body. Thus, apraxia may be due to damage to the left parietal or either frontal lobe.

A variety of tests are available to investigate for apraxia. Commonly used bedside tests include asking the patient to perform the following actions to command:

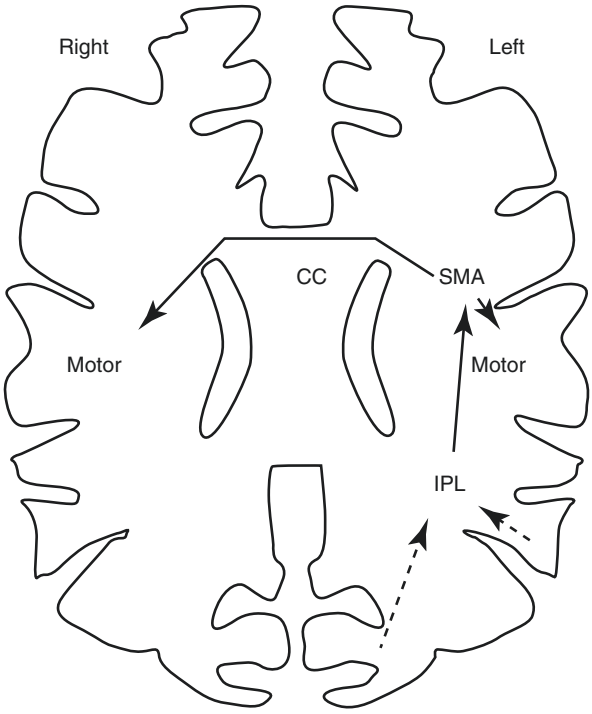

Fig. 4.1 Axial section of the brain showing simplified schematic of ideomotor apraxia. Multimodal sensory information is processed by the left inferior parietal lobule (IPL). This in turn activates motor programs in the left supplementary motor area (SMA) which project to the left motor cortex and via the corpus callosum (CC) to the right motor cortex

1. Wave goodbye.
2. Blow a kiss.
3. Pretend that they have a toothbrush in their hand, and use it to brush their teeth.
4. Pretend that they have a hammer, and use it to put a nail into a board.
5. Pretend that they have a brush, and use it to comb their hair.

Look for errors in positioning, orientation, sequencing, and timing. If the patient cannot perform these actions to command, demonstrate the actions, and ask the patient to imitate. It is also important to watch the patient use actual tools. In the hospital, readily available tools include pencils, forks, remote controls, and flashlights.

Apraxia may be due to vascular, traumatic, neoplastic, or degenerative disorders of the frontal or left parietal lobes. It is particularly common in patients with Alzheimer disease and corticobasal degeneration. The two most important applications of praxis testing are in patients with suspected corticobasal degeneration in whom apraxia is a prominent early finding and in patients with lesions of the corpus callosum in whom isolated left limb apraxia reflects disconnection between the left supplementary motor cortex and the right motor cortex.

Construction

Common tests of construction include drawing a house and drawing a clock. When a patient draws a house, study its general outline as well as specific details such as doors, windows, and chimneys. Patients who can draw the overall outline of the house but miss the details are more likely to have right hemisphere lesions, while those who draw a poorly outlined house with preserved details are more likely to have left hemisphere lesions. When analyzing a clock drawing, look first for evidence of poor planning such as crowding all the numbers on the right hand of the circle. Signs of perseveration (reflective of frontal lobe dysfunction) include repeating the same number several times or continuing to number the clock beyond "12." Patients with visuospatial deficits may place the numbers outside of the circle or draw the numbers in a spiral which closes in on itself. Visuospatial abilities and construction impairments tend to be more severe in patients with posterior cortical atrophy and dementia with Lewy bodies than in those with other forms of dementia.

Mental Flexibility, Set-Shifting, and Response Inhibition

Mental flexibility, including the ability to quickly switch between different cognitive tasks, is governed largely by the frontal lobes. The Luria test, Stroop test, and antisaccade test are three useful bedside tests for patients with suspected frontal lobe disorders.

Luria Test

In this test, the patient is instructed to form their hand into three simple shapes and then to tap a table or other flat surface. The most common sequence involves tapping the table first with the fist, then with the palm of the hand, and then with the side of the hand. Some patients with comprehension problems, apraxia, or severe

frontal lobe disorders have difficulty with even this first sequence. If the patient correctly learns and performs this sequence several times in succession, switch the sequence from *fist-palm-side* to *fist-side-palm*. Observe whether the patient is capable of switching to the second sequence, or whether they remain "stuck in set" and follow the original sequence.

Stroop Test

This test exists in a variety of forms, one of which consists of a grid of 30–40 words written in different colors, and is widely available online. The first several targets are names of colors written in the same color (e.g., the word "green" is written in green print). After eight to ten such targets, the words are written in different colors than the text (e.g., the word "green" is written in purple ink). To perform the Stroop test, first ask the patient to simply read the words. After they read through the entire list, instruct them to read the list from start to finish again, this time saying not the written word, but rather the color in which it is written. Patients with frontal dysfunction will perseverate by reading the word rather than the color. Even after corrected, they may continue to make the same kind of mistake.

Antisaccade Test

The antisaccade test assesses response inhibition. Validated, computer-based antisaccade tests are available, but no special equipment is needed to perform the test at the bedside [7]. To start, ask the patient to look directly at your face, and tell them that you will be holding up your hand on either the right or the left side and that they will need to look in the opposite direction of your hand. Start by alternating between targets on the left and right side. Some patients with frontal lobe disorders will not be able to inhibit their natural tendency to look towards your hand and will fail the test with the first stimulus. Other patients will become stuck in set and tend to look towards the same side after three or four stimuli have been shown on one side.

Processing Speed

Processing speed difficulties are signs of frontal lobe dysfunction and are often evident in the way the patient answers questions. A gestalt of processing speed may be estimated at the bedside by simple observation of the other parts of the mental status examination, particularly the "A" cancellation test described in Chap. 1 or by a Trails B-type test in which the patient is asked to "connect the dots" between alternating letters and numbers (Fig. 4.2).

Frontal Release Signs

The so-called frontal release signs or primitive reflexes are found in patients with moderate-to-severe dementia. The grasp sign is elicited by dragging a finger over the patient's opened palm and is positive when the patient clutches at the finger. The palmomental sign is observed when the chin puckers slightly upon gently stroking the palm. The snout or rooting reflex is present when a stroke of the cheek at the corner of the mouth results in a twitching of the mouth or lips. The glabellar sign is the failure to suppress continued blinking when the forehead is quickly tapped with an index finger and may be secondary to frontal or extrapyramidal pathology.

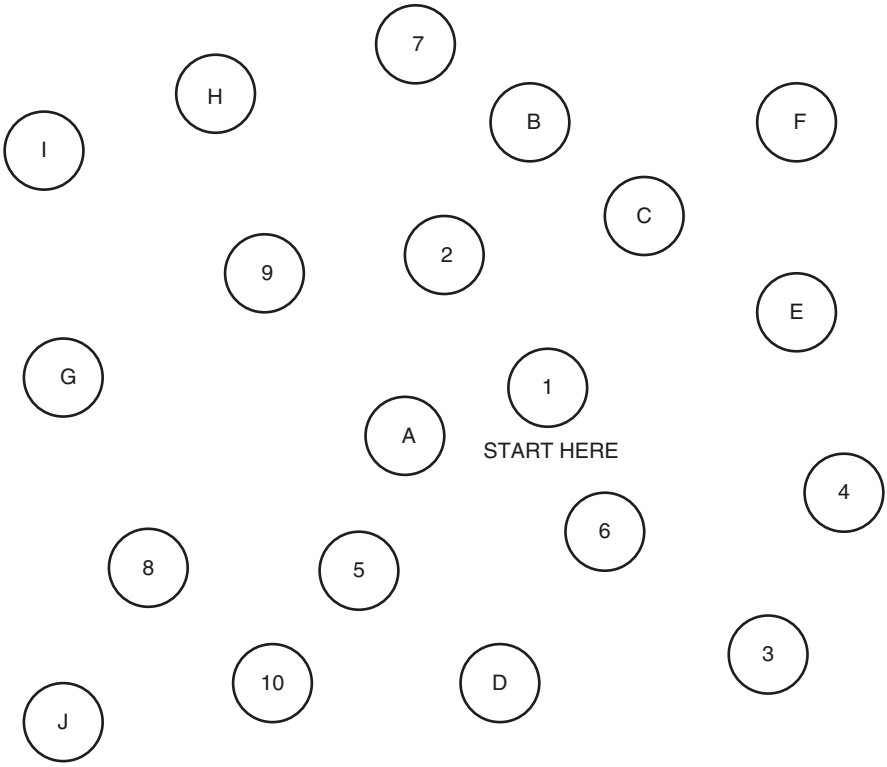

Fig. 4.2 Example of a Trails B-type test. Instruct the patient to begin at the number "1" and then to connect the dots between alternating letters and numbers. The correct sequence is, therefore, 1-A-2-B-3-C-4-D, etc. Observe the speed at which the patient performs the test and whether they can follow the instructions or instead connect the dots between consecutive numbers and letters. This test is sensitive to frontal lobe dysfunction

The General Neurologic Examination

The remainder of the neurologic examination should focus on finding deficits that establish the diagnosis of a specific dementia. As a general rule, patients with Alzheimer disease and frontotemporal dementia have otherwise normal neurologic examinations. The following is a brief summary of some of the more common and important examination abnormalities in demented patients.

Cranial Nerve Examination

A patient with frontotemporal dementia has difficulty following visual field examination instructions. When told to fix their attention on the examiner's nose, any stimulus such as wiggling fingers in the periphery will instantly draw their attention and prevent accurate visual field examination. Progressive supranuclear palsy leads to impaired downward saccade generation which corrects with oculocephalic maneuvers.

Motor Examination

Parkinsonism is a core feature of dementia with Lewy bodies, but rigidity and bradykinesia may be minimal or absent at the time of presentation. Myoclonus, though classically associated with Creutzfeldt-Jakob disease, can occur in any advanced dementia. Paratonia is an increased involuntary resistance to passive movement which worsens despite instructions to relax and is seen in frontal lobe disorders. Weakness, fasciculations, hyperreflexia, and other evidence of motor neuron disease are found in approximately 15% of patients with frontotemporal dementia.

Sensory Examination

Because polyneuropathies are common in the elderly, any sensory abnormalities should be interpreted cautiously, as they are usually unrelated to the cause of dementia. Vitamin B_{12} deficiency may lead to impaired vibratory sensation and joint position in the lower extremities. Corticobasal ganglionic degeneration may lead to asymmetric loss of higher cortical sensory functions such as graphesthesia and stereognosis.

Gait

Normal pressure hydrocephalus results in a gait abnormality characterized by poor initiation and short, slow steps with the feet narrowly spaced. This pattern is also observed in some patients with vascular dementia. Elderly patients commonly have a multifactorial gait disorder which does not actually reflect any specific dementia and may confuse the diagnostic process.

Diagnostic Testing

The diagnosis of dementia is made mostly from the history and mental status examination. Diagnostic testing is performed primarily to exclude reversible medical problems which masquerade as degenerative ones and, secondarily, to establish the diagnosis of a specific primary dementia.

Bloodwork

Every patient with suspected dementia should undergo tests of thyroid stimulating hormone, B_{12}, folate, and rapid plasma reagin. While the yield of these studies is quite low, they may disclose treatable causes of cognitive decline. Be cautious when attributing cognitive dysfunction to any of these laboratory findings, though, as test abnormalities do not necessarily exclude a degenerative dementia.

Structural Neuroimaging

It is essential to perform a neuroimaging study in all patients with dementia to exclude structural lesions such as tumors, abscesses, subdural hematomas, and

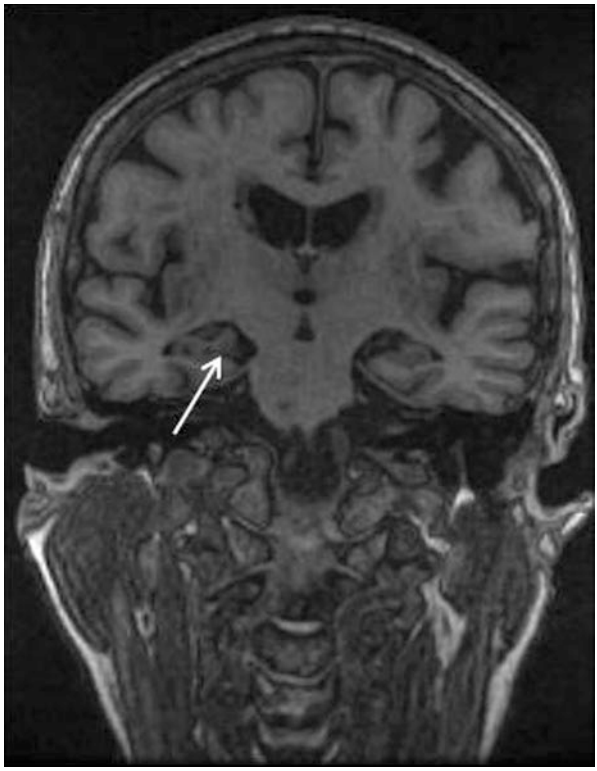

Fig. 4.3 Coronal MRI of the brain demonstrating medial temporal lobe atrophy in patient with Alzheimer disease

hydrocephalus. A non-contrast head CT is generally sufficient to screen for these problems. MRI, however, offers better neuroanatomic resolution than CT and helps with differential diagnosis. Findings in Alzheimer disease include medial temporal lobe atrophy, global volume loss, and secondary ventriculomegaly (Fig. 4.3). Frontotemporal dementia produces atrophy of the frontal and temporal lobes, more often involving the frontal lobes in patients with prominent behavioral features and the temporal lobes in patients with primary progressive aphasia (see below). Lewy body dementia may lead to mild, nonspecific global atrophy with relative sparing of the medial temporal lobes. Vascular dementia is associated with one of several patterns including leukoaraiosis (Fig. 4.4), cortical infarcts, and lacunar infarcts.

Functional Neuroimaging

Functional neuroimaging studies include positron emission tomography (PET), single-photon emission computed tomography (SPECT), functional MRI (fMRI), and magnetic resonance spectroscopy (MRS). They are usually reserved for distinguishing among the various forms of dementia in challenging cases, particularly in patients with early-onset dementia. PET and SPECT scans identify abnormalities of hypoperfusion and hypometabolism, respectively. Changes are seen in the temporal

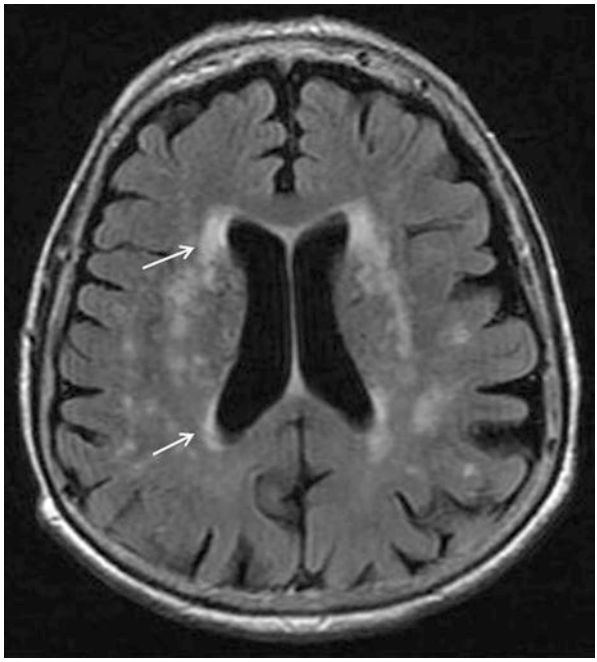

Fig. 4.4 This axial FLAIR MRI of the brain shows periventricular white matter hyperintensities in a patient with vascular dementia

and parietal lobes in Alzheimer disease, in the frontal and temporal lobes in frontotemporal dementia, and in the occipital lobes in dementia with Lewy bodies [8–10].

Amyloid PET imaging is best used for patients with atypical presentations or early-onset Alzheimer dementia [11–13]. It is not useful to determine dementia severity, in patients with cognitive complaints that are unconfirmed on mental status examination, or to verify Alzheimer dementia in older patients with otherwise typical features [14]. Negative amyloid PET studies predict a low likelihood of Alzheimer dementia, and should prompt investigation for other diagnoses. Positive tests, however, must be interpreted cautiously, as false positives range from 5% in subjects between 50 and 60 to more than 50% in patients older than 80 [15].

Lumbar Puncture

Lumbar puncture plays a limited role in evaluating dementia. It is most useful for patients with rapid progression, as it may disclose infectious, inflammatory, or neoplastic causes of cognitive decline. Lumbar puncture with timed gait analysis is an important step in evaluating NPH. Spinal fluid showing decreased amyloid β-42 and increased CSF tau may help to establish a diagnosis of Alzheimer disease in unclear cases [16].

Genetic Testing

Genetic testing is available for several different dementias, but is rarely employed in patients without clear familial histories of early-onset dementia. A review of the individual mutations and syndromes is beyond the scope of this text.

Causes of Dementia

Alzheimer Disease (AD)

AD is the most common form of dementia. The typical patient with AD is 65 or older and has a dementia characterized mainly by slowly progressive memory problems with anomia and apraxia. Early-onset and rapidly progressive forms of AD are less common but important variants, sometimes taking the form of posterior cortical atrophy or logopenic progressive aphasia. As the disorder progresses, memory deficits worsen, and essentially any cognitive domain may be affected. The diagnosis is established by history and mental status examination. Finding medial temporal atrophy on MRI supports the clinical diagnosis but is not identified universally [17]. In unclear cases, amyloid PET imaging and CSF amyloid and tau levels may be helpful to confirm the diagnosis.

The acetylcholinesterase inhibitors donepezil, rivastigmine, and galantamine (Table 4.2) are modestly effective in improving cognitive deficits, but do not alter disease progression. The most common adverse effects of these medications are nausea, vomiting, and diarrhea. These symptoms may be less severe with the rivastigmine patch than with one of the oral acetylcholinesterase inhibitors. The NMDA receptor antagonist memantine may be effective for patients with moderately severe disease, especially when used in combination with an acetylcholinesterase inhibitor. Side effects of memantine are uncommon and include dizziness and confusion. As AD progresses, medications are of limited value, and treatment

Table 4.2 Medications used to treat Alzheimer disease

Medication	Starting dose	Titration instructions
Donepezil	5 mg	Increase to 10 mg qd in 4–6 weeks
Rivastigmine	1.5 mg bid	Increase by 1.5 mg bid every 2 weeks to maximum dose of 6 mg bid
Rivastigmine patch	4.6 mg qd	Increase to 9.5 mg in 4 weeks
Galantamine	4 mg bid	Increase by 4 mg bid every 4 weeks to maximum dose of 12 mg bid
Memantine	5 mg qd	Increase to 5 mg bid in 1 week; 5 mg qam and 10 mg qpm in 2 weeks; and 10 mg bid thereafter

focuses on assistance with activities of daily living including bathing and eating and control of behavioral symptoms such as wandering and agitation. Ultimately, AD progresses, and patients with advanced disease require nursing home placement.

Dementia with Lewy Bodies (DLB)

DLB is the second most common of the degenerative dementias and, like AD, tends to occur in older people. The core clinical features of DLB are cognitive fluctuations (discussed above), visual hallucinations, and parkinsonism [18]. Visual hallucinations are initially nonthreatening and may take the form of people, animals, or brightly colored objects. As the disease progresses, the hallucinations may become more threatening. Parkinsonism is often subtle or absent in the early stages of DLB: if it is the main symptom at presentation, consider a form of parkinsonism other than DLB. REM sleep behavioral disorder in which the patient acts out their dreams may precede the development of other DLB symptoms, often by many years.

On mental status examination, episodic memory is relatively preserved in the early stages of the disease. Both semantic and phonemic fluency may be affected. Visuospatial impairments are more prominent than in patients with AD. Extrapyramidal findings are milder than those in Parkinson disease and tend to involve both axial and appendicular musculature. Tremor is usually absent.

There are no blood tests that are helpful in establishing the diagnosis of DLB. Neuroimaging is of modest value. CT and MRI of the brain help exclude the possibility of medial temporal atrophy suggestive of Alzheimer disease and vascular abnormalities consistent with vascular dementia. Dopamine transporter imaging may show low dopamine uptake in the basal ganglia in patients with DLB [19]. This study is useful in differentiating between patients with DLB and other dementias, but not differentiating between patients with DLB and other parkinsonian syndromes.

The acetylcholinesterase inhibitors donepezil, galantamine, and rivastigmine are often quite effective for cognitive and neuropsychiatric symptoms in DLB patients (Table 4.2) [20]. Levodopa and dopamine agonists are generally less useful for parkinsonism in DLB than they are in Parkinson disease. They should be reserved for severely debilitating motor symptoms because they may worsen hallucinations and other behavioral problems. In the early stages of DLB, hallucinations are not typically disturbing to the patient and therefore do not require treatment. When they do become disturbing, pimavanserin (17–34 mg qd), quetiapine (25 mg prn), and clozapine (6.25–25 mg qd) are the best options. Patients with DLB often react poorly to both typical and atypical antipsychotics.

Behavioral Variant Frontotemporal Dementia (FTD)

Behavioral variant FTD often is evaluated first by a psychiatrist rather than by a neurologist, as behavioral changes rather than memory impairment are the earliest

symptoms of the disorder. Patients with FTD tend to be younger than those with AD and DLB, typically developing symptoms in their 40s or 50s rather than in their 60s or later. Abnormal behaviors in FTD may be broadly clustered into socially inappropriate and withdrawn ones:

- Examples of socially inappropriate behavior include rude or lewd comments and uncharacteristic risk-taking behaviors such as excessive gambling or alcohol consumption. In the early stages, these socially inappropriate behaviors may be attributed to a mid-life crisis. The inappropriate patient is often evaluated and treated for bipolar or psychotic disorders before coming to neurological attention.
- Symptoms of withdrawal take the form of apathy, with little interest in work, family, or hobbies. The patient spends most of their time in bed, watching television, or simply staring into space. Personal hygiene is neglected. Patients with this FTD variant are usually evaluated and treated for depression before coming to neurological attention.

Other features of FTD include bizarre preferences for certain types of foods (especially sweets), hoarding behaviors, and obsession with generating artwork. Examination shows impaired mental flexibility, slowed processing speed, and early frontal release signs. Episodic memory is generally preserved in the initial stage of the disease, though it may be affected prominently when the medial temporal lobes are involved. Although the general neurologic examination is usually normal, approximately 15% of patients with FTD also have motor neuron disease (Chap. 10). When evaluating a patient for potential FTD, it is important to ensure that any new behavioral abnormalities are not due to pre-existing psychiatric disease or lifelong personality trends. Clandestine substance abuse also presents with symptoms that resemble FTD. MRI may disclose disproportionate frontal and temporal atrophy which helps to distinguish FTD from AD [21].

Pharmacologic treatment of FTD is often disappointing: acetylcholinesterase inhibitors are usually not effective and may actually worsen behavioral problems [22]. Selective serotonin reuptake inhibitors may help to control some of the compulsive symptoms. The activating serotonin-norepinephrine reuptake inhibitor venlafaxine may help with apathy and social withdrawal. Most patients with FTD, unfortunately, require close supervision and may need nursing home placement early in the course of their disease.

Vascular Dementia

The term “vascular dementia” encompasses three different disorders caused by cerebrovascular disease: multi-infarct dementia, subcortical white matter disease, and strategic infarct dementia.

Multi-infarct Dementia

Multi-infarct dementia is the classical form of vascular dementia. It is characterized by the stepwise accumulation of neurologic deficits from multiple, clinically obvious cerebral infarctions. While these strokes do not necessarily involve areas of the brain that are critical for memory, their cumulative effect is dementia. Mental status testing in patients with multi-infarct dementia resembles that of the other dementias (most commonly AD), but abnormalities on the general neurologic examination suggestive of prior infarctions such as hemiparesis and visual field cuts help to make the diagnosis. There is considerable overlap between multi-infarct dementia and AD, and distinguishing between the two on clinical or even radiologic grounds is often difficult. From a treatment perspective, the distinction may not necessarily be crucial, as patients with multi-infarct dementia, like those with AD, benefit from acetylcholinesterase inhibitors [23]. It is important to look for and treat risk factors for vascular disease such as hypertension, diabetes, and hyperlipidemia, though doing so does not improve cognitive symptoms.

Subcortical White Matter Disease

Subcortical white matter disease is known by a variety of names including Binswanger disease, periventricular white matter disease, and leukoaraiosis. It is characterized by the progressive accumulation of multiple, often clinically silent infarctions in the subcortical white matter. Patients most commonly present with bradyphrenia, impaired executive function, memory loss, and frontal gait abnormalities. Patients tend to resemble those with the withdrawn/abulic form of FTD or normal pressure hydrocephalus. Typical risk factors for vascular disease such as hypertension, hyperlipidemia, and diabetes are present.

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), secondary to a NOTCH 3 gene mutation is a rare cause of subcortical white matter disease in young and middle-aged people [24]. Vascular dementia secondary to CADASIL is often preceded by years of unexplained headaches. White matter hyperintensities are visible in the subcortical white matter, characteristically in the tips of the temporal lobes and external capsules.

Unfortunately, subcortical white matter disease responds poorly to any treatments, and care is largely supportive.

Strategic Infarct Dementia

Infarction of an area of the brain that is critical for memory is not strictly dementia, as it is acute in onset and deficits are static rather than progressive. Nonetheless, the persistent cognitive disorder that results from strategically located cerebral infarctions forces it to be considered here. Vascular territories associated with sudden-onset memory loss include the polar artery, paramedian thalamic artery, and the medial temporal branch of the posterior cerebral artery [25]. Deficits in strategic infarct dementia are usually fixed and nonprogressive. The mainstay of treatment is preventing stroke recurrence.

Normal Pressure Hydrocephalus (NPH)

The well-known clinical triad of NPH is dementia, urinary incontinence, and gait impairment. This simple summary, however, is misleading, and because the triad is rather nonspecific, it leads to many unnecessary referrals for "NPH evaluations." In short, many demented patients will develop both urinary incontinence and gait impairment as the disease progresses, and few of them will actually have NPH.

Although there is considerable heterogeneity of the clinical presentations of NPH, the features that are most consistent with the diagnosis are abulia (resembling that seen in FTD in some cases) and frontal gait abnormality. This frontal gait is characterized by slow initiation and shortened stride length to the point that the patient appears to be stuck to the floor by a magnetic force (Chap. 18). It is often incorrectly called ataxic or apraxic. This gait pattern may closely resemble that which is caused by arthritic degeneration of the spine, hips, and knees, or parkinsonism. The urinary incontinence of NPH has few features which distinguish it from incontinence of other causes.

Despite its relative rarity, consider NPH evaluation for patients with frontal dementia and frontal gait disorder, as NPH may respond to CSF shunting. All patients with NPH should undergo a CT scan or an MRI of the brain to document hydrocephalus (Fig. 4.5) and to exclude ventricular system outflow obstruction. Using an

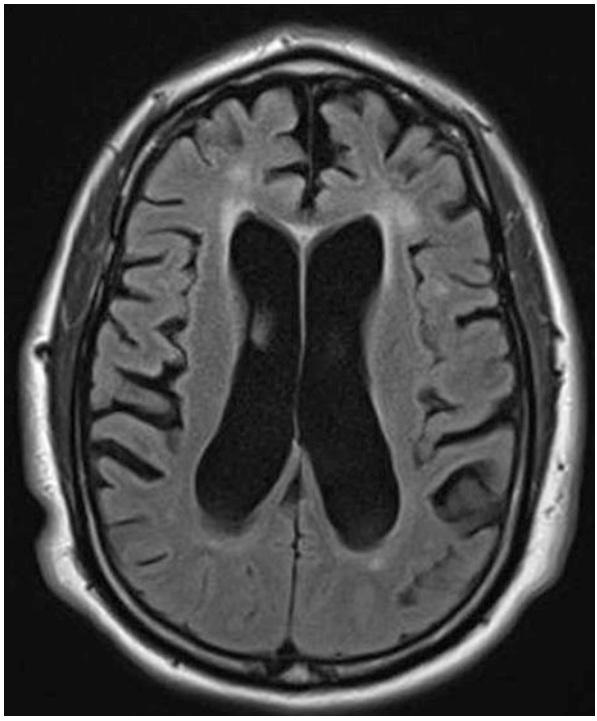

Fig. 4.5 Axial FLAIR MRI shows ventricular dilatation in a patient with normal pressure hydrocephalus

image to identify an Evans ratio (the ratio of the largest width of the frontal horns of the lateral ventricles to the inner table of the skull at the same level on an axial CT or MRI) of greater than 0.3 suggests the possibility of hydrocephalus. A modified version of the CSF removal test is the most common way to establish the diagnosis [26]

1. Admit the patient to the hospital.
2. Measure the amount of time and number of steps it takes to walk 60 feet. Repeat this walking test twice, encouraging the patient to do their best each time.
3. Remove 30–50 cc CSF by lumbar puncture.
4. Repeat the timed walking test immediately after and at 30 minute intervals up to 2 hours after lumbar puncture.

Improvement in the time and number of steps required to walk 60 feet predicts a positive response to cerebrospinal fluid shunting. Although it is difficult to quantify what actually constitutes an improvement, a consistent reduction in the time needed to cover 60 feet by 30% or more is strongly suggestive of the diagnosis. Monitoring mental status testing before and after lumbar puncture is less reliable than timed gait analysis. Unfortunately, the CSF removal test is subject to a large placebo effect. Placing a lumbar drain and extending the evaluation to include 24–48 hours of gait analysis may offer greater clarity than a single lumbar puncture does.

Consider ventriculoperitoneal shunting for patients with disease duration of less than 2 years, a positive CSF tap test, and a low burden of both cortical atrophy and periventricular white matter disease. In a systematic review of outcome of shunt surgery in NPH, 71% of patients experienced an improvement after shunting, with a greater likelihood of improvement identified in patients in more recent studies [27]. This statistic should be interpreted cautiously, because the patients and the methods used to make an NPH diagnosis and to monitor the outcome were heterogeneous. Prior to surgery, it is important to inform the patient and their family about possible complications of the procedure and of an indwelling shunt including meningitis, subdural hygroma or hematoma formation, and chronic headache.

Primary Progressive Aphasia (PPA)

Aphasia is a feature of many dementias, including Alzheimer disease, frontotemporal dementia, and corticobasal degeneration. PPA is a progressive dementia characterized by language deficits that are out of proportion to other deficits and dominate the early stages of the disease [28]. There are three generally recognized forms of PPA, though there is overlap among these and rigid classification systems often fail to diagnose a single subtype [29, 30]:

- Nonfluent progressive aphasia is characterized by slow, effortful speech with a lack of fluency, poor syntax, and relatively preserved comprehension. Patients demonstrate apraxia of speech (sound errors). Atrophy is usually seen in left inferior frontal and insular cortices.

- Semantic dementia is characterized by a fundamental loss of word meanings. Fluency is preserved, and comprehension is poor. The ability to name objects (confrontation naming) is impaired. Atrophy tends to affect the left anterior temporal lobe.
- Logopenic progressive aphasia is characterized by decreased fluency with relatively good syntax. There are long pauses while searching for words in spontaneous speech. Comprehension is good. Atrophy characteristically involves the left inferior parietal lobule and posterior temporal cortex. In most cases, logopenic progressive aphasia is an early-onset form of Alzheimer disease, and patients usually have positive amyloid PET scans.

The mainstay of PPA treatment is speech and language therapy. Over time deficits resembling behavioral variant FTD or Alzheimer disease may develop.

Posterior Cortical Atrophy

Posterior cortical atrophy is a syndrome of progressive decline in visual processing skills that characteristically begins in patients in their 50s or 60s [31]. There are problems with perceiving size, shape, and movement such as difficulty reading, judging distances when driving or parking, and getting on or off stairs or escalators. With time, this may progress into full-flown Balint syndrome (Chap. 5). Prosopagnosia (impaired facial recognition) may also develop over time. Episodic memory and language functions are usually preserved. Because the pattern of deficits is so unusual, patients with posterior cortical atrophy are often mistaken as having psychogenic disorders. MRI may show atrophy in the parietal and occipital lobes. FDG-PET imaging may show parieto-occipital hypometabolism [32]. Histopathological changes of Alzheimer disease are present in most cases. Patients with posterior cortical atrophy may derive mild benefit from acetylcholinesterase inhibitors and antidepressants. Resources used for blind or visually impaired patients are often helpful. With disease progression, it is important to assess driving safety and recommend cessation of driving when it becomes unsafe.

Alcohol and Dementia

Chronic alcohol abuse may result in nonspecific long-term cognitive changes. Korsakoff dementia is the classical alcohol-related dementia in which anterograde and retrograde amnesia are profound and out of proportion to other cognitive deficits. Korsakoff dementia often develops in patients recovering from Wernicke encephalopathy (Chap. 1). Because patients with Korsakoff dementia have severe memory deficits but preserved attention, they are prone to confabulation. They will fabricate explanations as to why they are in the hospital, relationships to the examiner, and current events. They actively seek environmental clues which sustain the impression that their memory is preserved. The presence of T2 hyperintensities in the mammillary bodies and medial thalami helps to establish the diagnosis of Korsakoff syndrome. Unfortunately, the memory deficits do not tend to improve, even with alcohol discontinuation and thiamine supplementation.

HIV Dementia

HIV dementia is the most severe form of HIV-associated neurocognitive disorder (HAND). It develops in approximately 1% of patients with HIV, but is decreasing in incidence with more widespread use of highly active antiretroviral therapy (HAART) [33]. HIV dementia is more likely to occur in patients with lower CD4 counts and AIDS. Presenting symptoms include psychomotor slowing and memory deficits, but as the disease progresses, any cognitive domain may be affected. The diagnosis is supported radiologically by finding characteristic confluent, subcortical white matter hyperintensities on MRI. Other sources of cognitive decline in patients with HIV such as progressive multifocal leukoencephalopathy, toxoplasmosis, and CNS lymphoma must be excluded. Treatment with HAART may improve cognitive symptoms or slow their progression.

Neurosyphilis

Tertiary neurosyphilis was a common cause of dementia in the preantibiotic era. It is now vanishingly rare in the United States, but should be considered as a possible source of dementia in patients with a history of syphilis (which usually precedes the dementia by 10 or 20 years) and in HIV-positive patients. Some suggestive findings include a schizophreniform presentation with strong delusions, dysarthria, and Argyll Roberston pupils (bilaterally small pupils which do not react to light but do constrict to near stimuli). Diagnostic testing in patients with dementia suspected to be secondary to syphilis should begin with a fluorescent treponemal antibody absorption (FTA-ABS) test and be confirmed with a serum RPR. Lumbar puncture should be performed in patients in whom the diagnosis cannot be confirmed with serologic testing. CSF shows a pleocytosis with a mildly elevated protein and a positive venereal disease research laboratory (VDRL). The standard treatment of GPI is penicillin (3–4 g IV q6h for 14 days), though the ability to reverse existing deficits is limited.

Dementia and Movement Disorders

Dementia frequently accompanies movement disorders, especially corticobasal degeneration, progressive supranuclear palsy, and Parkinson disease (Chap. 13). In general, these dementias are of the subcortical type, characterized by slow processing speed and difficulty with switching sets. Corticobasal degeneration, however, may produce a dementia with prominent cortical features, especially asymmetric limb apraxia.

Chronic Traumatic Encephalopathy

Multiple traumatic brain injuries may result in a form of dementia known as chronic traumatic encephalopathy (CTE). Originally recognized in boxers, and given the

name dementia pugilistica, CTE may be secondary to other forms of repeated head trauma, and the risk factors and clinical presentations for its development are an area of active inquiry. Patients develop short-term memory problems, but superimposed on these are depression, severe explosive mood swings, parkinsonism, substance abuse, and suicidal behavior [34]. Imaging findings that may help to confirm CTE include global cerebral atrophy, thinning of the corpus callosum, enlargement of the third ventricle, and cavum septum pellucidum.

Mild Cognitive Impairment (MCI) and Subjective Memory Impairment (SMI)

Because the pathological changes that lead to dementia begin gradually and accumulate over time, cognition exists on a continuum stretching from normal function, a transitional state, and then to full-blown dementia. The transitional state is mild cognitive impairment (MCI), in which cognitive abnormalities are present but do not yet meaningfully impact activities of daily living. Approximately 10% of patients with MCI will progress to Alzheimer disease (amnestic MCI) or to one of the other dementias (nonamnestic MCI) per year, far exceeding the 1% annual conversion rate of otherwise normal adults older than 65 [35].

An even earlier transitional state called subjective memory impairment (SMI) is characterized by subjective memory complaints and very mild impairments on cognitive testing. Although many patients with SMI are classified as the "worried well," approximately 2–3% of SMI patients convert to AD annually [36, 37].

Acetylcholinesterase inhibitors do not clearly delay progression of MCI or SMI to dementia, although they are commonly prescribed [38]. Cognition in patients with MCI may revert back to normal on subsequent testing, likely secondary to diurnal cognitive fluctuation between testing sessions or variation in measurement techniques [39].

Pseudodementia

Several conditions produce progressive cognitive deficits resembling dementia. When a patient presents with progressive cognitive decline, it is important to consider these mimics of dementia, as they may respond to treatment.

Depression

Cognitive complaints, especially memory loss, are common in patients with depression. It is a classical teaching, but not a universal truth that patients with depression are aware of their memory problems, unlike patients with dementia, who lack awareness. Using the mental status examination to separate patients with dementia from those with depression is often challenging. Inquiring directly about depression

may bring the problem to light in some cases. In others, a screening questionnaire such as the Beck Depression Inventory or similar tool may be helpful [40]. Psychiatric consultation and antidepressants may improve symptoms of depression and the associated cognitive complaints.

Obstructive Sleep Apnea (OSA) and Other Sleep Disorders

Patients with obstructive sleep apnea complain of difficulty concentrating during the daytime, an urge or need to take naps, snoring, and morning headaches. In some cases, memory difficulties may be the chief complaint [41]. Physical examination findings suggestive of OSA include obesity, increased neck circumference, and a crowded oropharynx. Patients with unexplained cognitive complaints should undergo screening for OSA or other sleep disorders with a polysomnogram and formal sleep medicine consultation. Noninvasive positive pressure ventilation, if used properly, may reverse many of the cognitive complaints associated with OSA.

Pain

Patients may find it difficult to sleep or concentrate due to chronic, unresolved pain, or may have cognitive difficulties because they require high doses of pain medications. Because successful pain treatment or modification of existing pain treatment regimens may lead to an improvement in mental status, it is a good idea to review any ongoing pain symptoms and medications with all patients referred for cognitive complaints.

Adult Attention Deficit Hyperactivity Disorder (ADHD)

Although ADHD is a disorder that begins in childhood, it may go undiagnosed until adulthood, especially in people who grew up before ADHD was recognized with great frequency. ADHD persists into adulthood in about 50% of children who have the diagnosis. It is perhaps the most common diagnosis in patients who are evaluated for cognitive dysfunction in their 20s and 30s. Patients with ADHD are impulsive, are disorganized, and have difficulty concentrating. They may complain of memory problems, but their real problem is with sustaining attention. The history and a general observation of the patient usually is sufficient to make the diagnosis. Screening questionnaires such as the Adult ADHD Self-Report Scale are helpful in establishing a diagnosis and assessing response to treatment over time [42]. Cognitive-behavioral therapy plays an important role in treatment of ADHD. The norepinephrine transport inhibitor atomoxetine (started at 40 mg qd, titrated up to 80 mg qd) is often the first option for treating ADHD, as it has fewer side effects and a lower addiction potential than stimulants do. For patients who require stimulants,

options include methylphenidate, dexmethylphenidate, dextroamphetamine/amphetamine mixed salts, and lisdexamfetamine. Longer-acting formulations are less likely to be abused. Side effects of stimulants include headaches, weight loss, irritability, and palpitations. Antidepressants including bupropion, venlafaxine, and paroxetine can be used for patients who do not respond to atomoxetine or stimulants.

Medication Side Effects

A number of medications may produce cognitive side effects, often when used chronically by older patients. Examples include antidepressants, anticonvulsants, antipsychotics, mood stabilizers, opioids, and sedatives. Trials of discontinuing or switching the potential culprit to an alternative medication are indicated for these patients.

Conversion Disorders and Malingering

These two psychiatric disorders may mimic any neurologic symptom. In many cases, neuropsychological evaluation is necessary to tease apart these psychiatric disorders from neurologic ones.

Postconcussion Syndrome

Mild traumatic brain injury (TBI), defined as a head injury that produces a loss of consciousness of less than 30 minutes' duration, is associated with a variety of neuropsychological complaints including headache, dizziness, memory loss, irritability, and inattention [43]. The term postconcussion syndrome is often used to describe this cluster of complaints, though most patients lack one or more elements of the complete "syndrome." The mechanism of chronic postconcussive symptoms is unclear, but axonal injury, secondary gain including unresolved legal disputes, and pre-existing or superimposed psychiatric disorders such as anxiety and depression all contribute [43]. Most patients with mild traumatic brain injury have good prognoses, recovering within 1–2 weeks. Some patients continue to experience symptoms at 1 month, 3 months, or even more chronically. Accurate statistics are difficult to provide because similar complaints are also present in a substantial proportion of patients without a recent history of head trauma [44]. Although cognitive rehabilitation may help, there is no single treatment for the postconcussion syndrome, and the individual complaints must be isolated and treated independently. Resolution of legal matters and successful treatment of depression are important steps to maximize the chance for a good outcome.

Subacute and Rapidly Progressive Dementias

Although dementia is operationally defined as a disorder lasting for at least 6 months, a group of patients declines more rapidly over a period of weeks to just a few months. In many cases, histories provided by the family are inaccurate, and symptoms have been present for more than 6 months but ignored or compensated for by others. The diagnosis may ultimately prove to be one of the more common degenerative dementias such as Alzheimer disease or vascular dementia, but the following conditions must be considered first when evaluating a patient with rapidly progressive dementia:

Creutzfeldt-Jakob Disease (CJD)

The prion disease CJD is the prototypical rapidly progressive dementia. In addition to producing any pattern of cognitive deficits, patients with CJD may have a variety of other signs and symptoms including seizures and abnormalities of the cerebellar, pyramidal, and extrapyramidal systems. CJD develops years to decades after exposure to infected brain tissue such as dural grafts, human pituitary hormones, or improperly sterilized neurosurgical equipment. In most patients, however, the exact source cannot be identified. Beyond the cognitive deficits, the best-known sign of CJD is myoclonus (see Chap. 14). If it is not visible at rest, myoclonus or an enhanced startle response may be elicited by suddenly clapping your hands or dropping your keys to the ground. Bear in mind, though, that myoclonus may be a feature of any dementia in its advanced stages and is not pathognomonic for CJD. The single best noninvasive diagnostic test for evaluating CJD is a diffusion-weighted MRI of the brain showing diffusion slowing in the cortex and basal ganglia (Fig. 4.6) [45]. Other findings of CJD include EEG showing periodic sharp waves with a biphasic or triphasic morphology, elevated CSF 14-3-3 protein in the CSF, elevated CSF neuron-specific enolase in the CSF, and abnormal CSF real-time quaking-induced conversion (RT-QuIC). Brain biopsy showing spongiform changes and abnormal prion protein histochemistry make the diagnosis when noninvasive tests fail to do so. Unfortunately, there is no effective treatment for CJD, and patients have a uniformly fatal outcome, generally within several weeks to months of diagnosis.

Hashimoto Encephalopathy

Hashimoto encephalopathy is a rapidly progressive dementia which clinically resembles CJD. Originally described in patients with hypothyroidism, the symptoms are not the result of thyroid hormone abnormalities, but are more likely

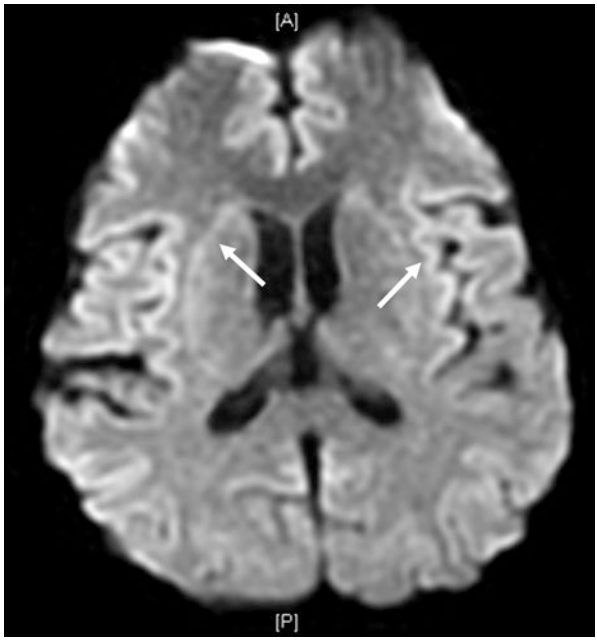

Fig. 4.6 Diffusion-weighted MRI shows slowing (hyperintense signal) throughout the cerebral cortex and basal ganglia

secondary to an autoimmune process [46]. Systemic symptoms suggestive of thyroid dysfunction are usually not present, and the degree of cognitive dysfunction is not correlated with serum thyroxine or thyrotropin levels. The diagnosis of Hashimoto encephalopathy is established by finding antithyroid peroxidase or antithyroglobulin antibodies. Be conservative in making the diagnosis, as some patients with thyroid antibodies may have another degenerative condition including CJD or a paraneoplastic disorder (Chap. 1). MRI may show nonspecific cerebral atrophy. CSF analysis characteristically shows elevated protein, with a small proportion of patients demonstrating a lymphocytic pleocytosis. Hashimoto encephalopathy responds to treatment with corticosteroids, often dramatically: some patients respond to a single course of methylprednisolone 1 g/d × 3–5 days, others require occasional repeat infusions, and some need steroids chronically [47].

Leptomeningeal Metastasis and Limbic Encephalitis

Cancer may produce subacutely progressive cognitive dysfunction by direct infiltration of the nervous system or via a paraneoplastic mechanism, as discussed in Chap. 1. CNS lymphoma is an infrequent cause of dementia but a culprit that must be considered in patients with rapidly progressive cognitive decline and atypical cerebral white matter changes.

Evaluation of Undiagnosed Rapidly Progressive Dementia

Most patients with rapidly progressive dementia will not have Creutzfeldt-Jakob disease, Hashimoto encephalopathy, or a readily detectable cancer-related process. Blind brain biopsy can be considered in undiagnosed patients, though it is diagnostic in just over half of patients who undergo the procedure [48]. PET scans to look for undiagnosed neoplasms may be of help to reach a diagnosis in some patients. Ultimately, many patients with rapidly progressive dementia have one of the more common primary dementia syndromes.

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Visual Loss and Other Visual Disturbances

5

Neuroanatomy

A brief discussion of the neuroanatomy of the visual system (Fig. 5.1) is necessary to understand how to approach the patient with visual loss. Light enters the eye through the cornea and passes through the anterior chamber, the lens, and the vitreous to reach the retina. Images are projected upside down and backwards onto the retina. The inferior temporal retina, therefore contains the image of the superior

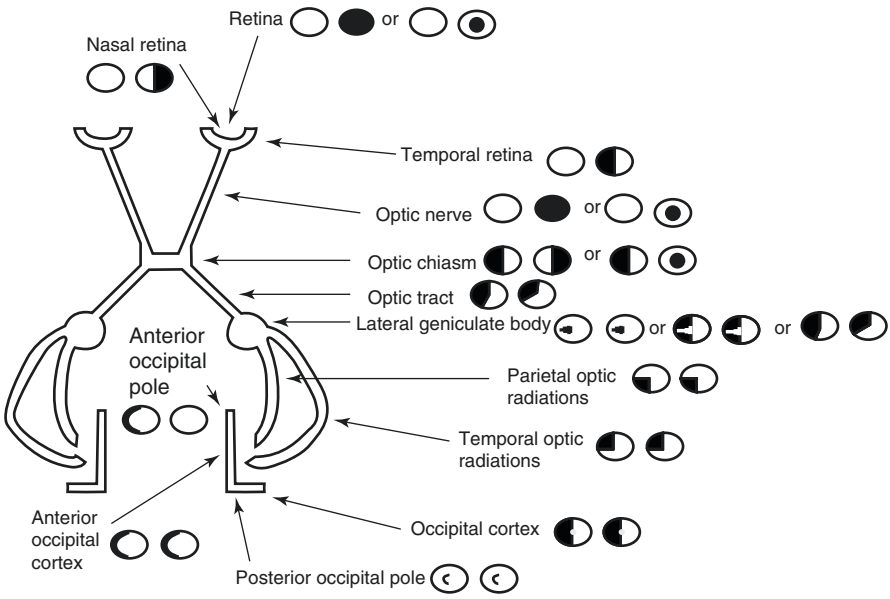

Fig. 5.1 Schematic of visual system neuroanatomy and common visual field defects. See text for more details

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nasal part of space. The optic nerve enters the retina at the optic disc. Lateral to the optic disc is the macula, the center of which is the fovea, the area of greatest visual acuity. The nasal optic nerve fibers (those which see the temporal field of vision) decussate in the optic chiasm, while the temporal optic nerve fibers remain uncrossed. The optic chiasm gives rise to the optic tracts. The left optic tract contains the representation of the right half of visual space: the temporal field of the right eye and the nasal field of the left eye. The optic tracts send fibers to the pretectal nucleus of the midbrain and the lateral geniculate body of the thalamus. The pretectal fibers synapse in the Edinger-Westphal nucleus of the oculomotor nerve (Chap. 7) and decussate in the posterior commissure to reach the contralateral pretectal nucleus. The lateral geniculate body sends fibers to the occipital cortex via the optic radiations. The temporal optic radiations contain fibers from the superior visual fields and are known as Meyer's loop, while the parietal optic radiations contain fibers from the inferior visual fields. The posterior occipital cortex contains the representation of macular vision. Progressively more anterior parts of the occipital cortex contain progressively more peripheral representations of visual space. The anterior part of the visual cortex contains a representation of the extreme temporal periphery from the contralateral eye (the "temporal crescent") but lacks a homonymous nasal representation from the ipsilateral eye. The occipital cortex sends projections to the ipsilateral visual association cortices. These may be roughly divided into the "what" cortex of the temporal lobe which processes content and the "where" cortex of the parietal lobe which processes spatial information.

History

Most patients with visual loss have ophthalmologic problems such as cataracts, glaucoma, and macular degeneration. With some exceptions such as angle closure glaucoma and retinal detachment, most of these conditions tend to develop slowly over months to years. The neurologic conditions that affect vision, however, develop more quickly over a course of days, hours, or even minutes and often lead to evaluation in the emergency room. The most important elements of the history, beyond the tempo of symptom development, are whether pain accompanies visual loss and the exact pattern of visual field loss. This pattern may be established to some degree by the history, but in most cases, the examination is more helpful. In some instances, it may be useful to "cheat" slightly by beginning with a brief examination in order to tailor the history appropriately.

Examination of the Visual System

Visual Acuity

The first step in examining the visual system is to measure visual acuity in each eye. In order to eliminate refractive errors, the patient should wear their eyeglasses or

contact lenses when their acuity is being tested. If they do not have their glasses, eliminate refractive errors by using a pinhole occluder or by poking tiny holes through an index card.

Pupillary Reactions

The anatomy of pupillary reactions is discussed in Chap. 7. In a patient with visual loss, examine the pupils in both light and dark. Make note of pupil size and regularity. Use a sufficiently bright flashlight when examining pupillary reactions: if the pupils constrict and then dilate quickly (hippus), the intensity of the light is probably too low. Observe for both the direct (pupillary reaction in the eye in which the light is shined) and consensual (pupillary reaction in the eye in which the light is not shined) reactions.

Relative Afferent Pupillary Defect (RAPD)

RAPD almost always indicates an ipsilateral optic nerve lesion (Fig. 5.2). To test for an RAPD, examine the patient in a dimly lit room with a bright flashlight. Instruct

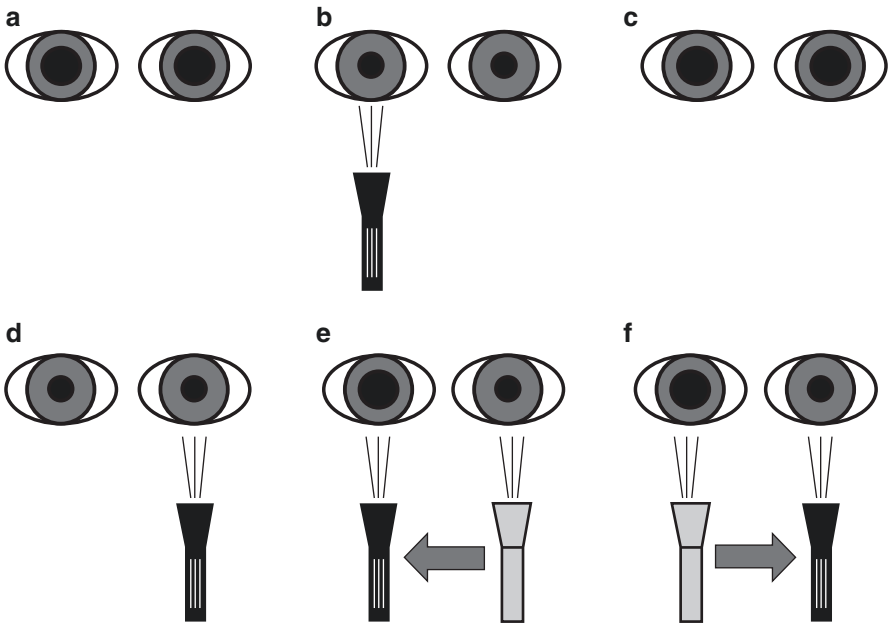

Fig. 5.2 Testing for a right relative afferent pupillary defect. Note that in Fig. 5.2e and f, the consensual light reaction is not shown. See text for more details

the patient to focus on a distant target and shine the light into their eyes from below eye level. For a patient with a right RAPD:

1. At rest, both pupils should be equal (Fig. 5.2a).
2. Shine the light in the right eye for approximately 3 seconds, and observe the direct and consensual pupillary reactions (Fig. 5.2b).
3. Remove the light and allow the pupils to dilate (Fig. 5.2c).
4. Shine the light in the left eye for approximately 3 seconds, and observe the direct and consensual pupillary reactions (Fig. 5.2d).
5. Swing the light to the right eye and watch its reaction. If the pupil dilates even slightly on the right, the patient has a right RAPD (Fig. 5.2e). The left pupil should also dilate (not shown).
6. Swing the light back to the left eye and look for constriction of the left pupil (Fig. 5.2f). The right pupil should also constrict (not shown).

It is important to swing the flashlight back and forth several times in order to verify that an RAPD is indeed present.

Color Discrimination

The next step in assessing visual loss is to test color discrimination, as color vision is often lost early in patients with optic nerve disease. The most sensitive way to do this at the bedside is with Ishihara color plates. If these are not available, a simple way to examine for gross color vision defects is to test for red desaturation. Hold a bright red object in front of each eye in sequence, making sure that the background against which it is viewed is consistent, and ask the patient to describe the color of the object and to note any color differences between the eyes. A patient with an optic neuropathy will perceive a bright red object as pink, black, brown, or washed out in appearance.

Visual Field Examination

Most gross visual field defects that bring a patient to acute neurological attention are detectable with bedside confrontation testing. Perimetry may be required to detect more subtle deficits.

Central Visual Fields

Examine the visual fields in each eye independently. First, instruct the patient to look directly at your nose, and test their central visual fields by asking them whether any parts of your face appear to be missing or blurred. Another good test of central vision is to ask the patient to trace their visual field deficit onto an Amsler grid or piece of graph paper.

Peripheral Visual Fields

Start by placing yourself approximately 3 feet away from the patient. Instruct them to close one eye and to look directly at your nose. For the first part of the examination, tell them that you will show one or two fingers and that it is their job to tell you how many they see. Quickly flash one or two fingers in each of the four quadrants of the visual field in succession. This is a gross test of each of the peripheral visual fields. Next, map out the visual fields using a red pinhead. Remind the patient yet again that they should be focusing on your nose, and tell them to report the exact instant at which they perceive the redness of the pin. Sweep the pin from the periphery to the center of the visual field. If the pin is halfway between their viewing perspective and your own, you should appreciate its redness at approximately the same time as the patient.

Visual field examination is often time-consuming, and subtle deficits may be missed if the fields are examined too hastily. Conversely, most visual field defects indicative of serious neurologic disease are obvious upon gross examination. Screening for the following common patterns (Fig. 5.1) of visual field loss is helpful at the bedside:

- Monocular visual loss. This is the expected pattern of visual field loss in a patient with dysfunction of the eye or optic nerve.
- Central scotoma. In this pattern, the central portion of vision is lost while the periphery is preserved. It too implies dysfunction of the retina or optic nerve.
- Monocular altitudinal defect (not shown). Either the top or bottom half of vision is lost. This pattern suggests retinal ischemia.
- Bitemporal hemianopsia. The temporal half of vision is lost in both eyes. This is the classical pattern produced by disorders of the chiasmal region such as pituitary adenomas.
- Junctional scotoma. A junctional scotoma occurs when a mass at the optic chiasm compresses the ipsilateral optic nerve and the decussating fibers from the contralateral nasal portion of the optic nerve. The result is ipsilateral monocular visual loss (or a central scotoma) and a contralateral temporal field cut.
- Homonymous hemianopsia. This is the typical pattern of post-chiasmatic lesions: the same "half" of vision (e.g., right nasal field and left temporal field) is affected in both eyes. Post-chiasmatic lesions that are relatively more anterior (e.g., in the optic tracts and anterior radiations) tend to have less left-right symmetry than those that are more posterior (e.g., the posterior radiations and occipital lobes).
- Lateral geniculate body (LGB) lesions. Lesions of the LGB may produce contralateral homonymous hemianopia. However, lesions of the portion of the LGB perfused by the anterior choroidal artery may produce a homonymous hemianopia with a spared horizontal central wedge, while lesions of the portion of the LGB perfused by the posterior choroidal artery may cause loss of the central

wedge with sparing of the periphery. These deficits, however, are not universally present in patients with choroidal artery infarctions and are quite difficult to map out at bedside.

- Upper quadrantanopsia. This is the loss of the superotemporal field in the contralateral eye and the superonasal field in the ipsilateral eye. This is the characteristic field cut produced by lesions of the temporal optic radiations.
- Lower quadrantanopsia. Loss of the inferotemporal field in the contralateral eye and the inferonasal field in the ipsilateral eye is the characteristic field cut of the optic radiations within the parietal lobe.
- Macular-sparing homonymous hemianopsia. Occipital lesions classically lead to homonymous hemianopsia with sparing of macular vision. The neuroanatomy of macular sparing is controversial. Possible, but not completely satisfactory, explanations include a dual blood supply (posterior cerebral and middle cerebral arteries) of the occipital cortex subserving foveal vision and bilateral representation of the foveal vision in the occipital cortex.
- Temporal crescent defects. Anterior occipital lesions produce loss of vision in the extreme temporal periphery of the contralateral eye while sparing vision in the ipsilateral eye. This is an extremely rare visual field defect.

Funduscopic Examination

The final step in examination of the patient who complains of visual loss is funduscopy. Accurate funduscopic examination is essential to the diagnosis of monocular visual loss and may also be helpful in patients with binocular visual loss. It is important to visualize the fundi in the dark or to pharmacologically dilate the pupils. Important funduscopic abnormalities in patients with visual loss include:

- Papilledema. This is the funduscopic finding that accompanies increased intracranial pressure. See Chap. 19 and Fig. 19.2 for additional details.
- Central retinal artery occlusion. In the hyperacute setting, the optic disc appears normal or may show boxcar segmentation of blood within the retinal vessels. After approximately 1 hour, the retina takes on a white appearance. The vascular choroid (supplied by the posterior ciliary artery) shines through at the fovea, producing the classical cherry-red spot. Dull white (platelet-fibrin embolus) or bright yellow (cholesterol or Hollenhorst plaque) retinal emboli may be detected in the branches of the central retinal artery.
- Central retinal venous occlusion. The funduscopic appearance of central retinal venous occlusion is difficult to miss: the disc is blurred, and the periphery of the fundus is smeared with hemorrhages.
- Optic disc pallor. This pattern reflects chronic disease of the optic nerve.
- Abnormal cup/disc ratio. A small cup/disc ratio is often seen in the fellow eye of a patient with nonarteritic ischemic optic neuropathy. A large cup/disc ratio is seen in open-angle glaucoma.

Monocular Visual Loss

The most common neurologic etiologies of monocular visual loss are inflammatory and ischemic processes. Consider these etiologies not only in patients with unilateral visual loss but also in patients in whom vision is lost in each eye in sequence.

Optic Neuritis

Idiopathic Optic Neuritis

Optic neuritis is a common cause of acute-to-subacute visual loss in young people, especially young women. Monocular visual loss occurs over a period of several days and ranges from mildly reduced acuity to complete blindness with no light perception. There is mild periocular pain with eye movement. Phosphenes are brief flashes of light, often connected to eye movement, that are common in optic neuritis. Funduscopic examination is usually unremarkable in the acute setting, as most patients have retrobulbar optic neuritis. Most patients with optic neuritis have a complete or near complete recovery of vision within a month. Further evaluation and treatment of optic neuritis is discussed in Chap. 22.

Atypical Optic Neuritis

Less common inflammatory and autoimmune causes of optic neuritis include sarcoidosis, Sjogren syndrome, systemic lupus erythematosus, and Behcet disease. These conditions are best distinguished from typical optic neuritis by the accompanying systemic symptoms. Devic disease (neuromyelitis optica) is characterized by the combination of optic neuritis and transverse myelitis and is discussed further in Chap. 22.

Ischemic Optic Neuropathies

Temporal Arteritis

Temporal arteritis (giant cell arteritis) is a systemic vasculitis that may result in blindness due to ischemia of the retina, choroid, or optic nerve. Patients with temporal arteritis are always older than 50, with a mean age of onset of about 70. Symptoms in addition to visual loss that suggest the diagnosis include headache, jaw claudication (pain with chewing), and scalp tenderness. Polymyalgia rheumatica, characterized by fever and aches in the shoulders and hips, accompanies temporal arteritis about half the time. Visual loss occurs in both eyes in up to 50% of patients: in approximately 1/3 of these, visual loss affects the fellow eye within 1 day, in another 1/3 within 1 week, and in the remaining 1/3 within 1 month. The classic funduscopic appearance is a pale, swollen optic nerve head, sometimes accompanied by small hemorrhages near the disc margin. Central retinal artery occlusion may also occur. Funduscopic examination may be normal in patients with temporary visual loss. Diplopia occurs in a small minority of patients. In patients

with suspected temporal arteritis, check the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) immediately so that corticosteroids can be started [1]. A normal ESR for a man is his age divided by two and for a woman her age plus ten divided by two [2]. The main purpose of steroid treatment is to prevent visual loss in the fellow eye and other systemic symptoms, because recovery from existing visual loss is rare. In order to give the patient the best chance of preserving their vision, start intravenous methylprednisolone 1 g IV qd × 3 days or prednisone at 60–80 mg qd as soon as you consider the diagnosis. Because the morbidity of chronic steroid administration is high, it is necessary to arrange for temporal artery biopsy to confirm the diagnosis in almost all cases. Pathologic changes of temporal arteritis remain visible on biopsy for up to 2 weeks after initiating steroids [3]. Ultrasound may be a useful investigation in some patients, showing a dark, hypoechoic signal at the vessel wall, the so-called "halo sign." In patients with confirmed temporal arteritis, the tapering of steroids should start after 1 or 2 months and continue very slowly. Most patients require at least a low dose of steroids for approximately a year after starting treatment. The addition of the IL-6 inhibitor tocilizumab may be helpful in reducing temporal arteritis recurrence and the total steroid dose [4].

Nonarteritic Ischemic Optic Neuropathy (NAION)

NAION, the most common anterior ischemic neuropathy, is characterized by painless monocular visual loss developing over hours to days [5]. It tends to affect older patients, and many of these patients have risk factors for vascular disease. NAION presents in a similar fashion to temporal arteritis, but several clinical clues help to distinguish between the two conditions. The degree of visual loss is typically milder in NAION than it is in patients with temporal arteritis. Patients lack pain, headache, and other symptoms of systemic disease. Binocular visual loss occurs in approximately 20% of patients, a much lower frequency than in temporal arteritis, and does not occur as suddenly. The NAION optic disc appears hyperemic, and the unaffected eye often has a crowded optic nerve head with a small cup-to-disc ratio. ESR and CRP are normal. Fluorescein angiography is a useful test in distinguishing NAION from temporal arteritis: choroidal perfusion is normal in NAION but delayed in patients with temporal arteritis [6]. Unfortunately, there is no clearly proven therapy for NAION, and there are no interventions that reduce the probability that the contralateral eye is affected. Risk factors for vascular disease should be addressed. Many patients will demonstrate some improvement in visual acuity, though this improvement may be modest.

Less Common Optic Neuropathies

Structural Optic Neuropathies

Compressive or infiltrative causes of optic neuropathies include trauma, tumor, abscess, or inflammatory lesions. It is important to recognize these causes of monocular visual loss quickly, as they require immediate consultation with an orbital surgeon.

Toxic and Nutritional Optic Neuropathies

Methanol and ethylene glycol intoxication produce fulminant encephalopathies associated with severe bilateral optic neuropathies and a variety of systemic symptoms. Management of intoxication with these substances requires input from multiple specialists including toxicologists and nephrologists. Ethambutol, disulfiram, and amiodarone are the most common medications that produce toxic optic neuropathies. Vitamin B_1 and B_{12} deficiencies may also cause optic neuropathies.

Inherited Optic Neuropathies

Autosomal dominant and recessive optic neuropathies generally come to clinical attention in children but may manifest for the first time in adults.

Leber hereditary optic neuropathy (LHON) is a mitochondrial disorder that affects mostly men and may develop in young adulthood or early middle age [7]. It is characterized by painless, subacutely progressive visual loss that is often bilateral. Some patients with LHON develop other central nervous system abnormalities which may lead to a clinical picture resembling multiple sclerosis. The diagnosis of LHON is confirmed by identifying causative NADH dehydrogenase mutations. Unfortunately, there is no effective treatment for LHON. The mainstays of therapy include antioxidant cocktails consisting of vitamin C, vitamin E, and coenzyme Q and avoidance of tobacco and foods that contain high levels of cyanide such as cassavas. Prognosis for visual recovery is poor.

Retinal Ischemia and Infarction

The ophthalmic artery is the first intracranial branch of the internal carotid artery. It gives rise to several branches including the central retinal and posterior ciliary arteries. The central retinal artery supplies blood to the retina via smaller branch arteries. The posterior ciliary arteries supply blood to the choroid, ciliary body, and iris. Reduced blood flow to the ophthalmic, central retinal, or branch retinal arteries may result in acute visual loss.

Central retinal artery occlusion is characterized by acute, painless, monocular visual loss. Transient ischemic attack involving the central retinal artery classically produces amaurosis fugax, in which the patient experiences visual blurring as if a shade is being pulled over the eye. Patients may also describe a constriction of vision or patchy visual loss. Amaurosis fugax usually lasts between 5 and 20 minutes and resolves spontaneously. Branch retinal artery infarction causes visual loss limited to the visual field sector that the artery perfuses.

Ophthalmic artery infarction presents in a manner similar to central retinal artery occlusion but may be associated with orbital pain and mydriasis due to accompanying infarction of the ciliary ganglion or iris sphincter. Because the choroid is also infarcted, the cherry-red spot (see above) is usually absent in ophthalmic artery infarction. Unfortunately, there is no clearly effective treatment to reverse or reduce visual loss from central retinal or ophthalmic artery occlusion [8]. Evaluation and treatment focuses on preventing cerebral ischemia secondary to cardiac, internal carotid artery, or end artery disease (Chap. 21).

Migraine Aura Without Headache

Approximately half of patients with migraine aura (Chap. 19) will have some element of visual loss [9]. Aura occurs without a subsequent headache in a small minority of these patients. The aura typically develops over a few minutes and lasts for up to half an hour. Migraine aura without headache should be considered a diagnosis of exclusion unless the patient has a strong prior history of migraine with visual aura: all patients require a detailed evaluation for other, more serious causes of visual loss.

Angle Closure Glaucoma

Although the diagnosis of angle closure glaucoma is most often made by ophthalmologists, emergency room physicians, and internists, it occasionally comes to the attention of a neurologist. A patient with angle closure glaucoma usually has a red eye and appears to be in acute distress, clutching and covering the affected eye. Visual acuity is markedly decreased, and the pupil is unreactive and in midposition. Unilateral arcuate (arc-shaped) field defects that do not cross the horizontal midline are suggestive of glaucoma and not seen in the primary neurologic causes of visual loss. Measure intraocular pressure, and obtain ophthalmological consultation as soon as angle closure glaucoma is suspected.

Bitemporal Hemianopsia and Junctional Scotoma

Bitemporal hemianopsia and junctional scotoma are caused by extension of sella turcica pathology into the adjacent optic chiasm. In many cases, visual loss is gradual, and the patient may not report any problems beyond slight visual blurring. Headaches from mass lesions in this region are also common and result from stretching of the diaphragma sellae. Because most of the pathology that involves the optic chiasm also involves the pituitary gland, accompanying endocrine disturbances are frequent. Common causes of sellar lesions in adults include pituitary adenoma, craniopharyngioma, and meningioma (Chap. 23). Uncommon sellar lesions include aneurysms of the circle of Willis, adenohypophysitis (classically secondary to sarcoidosis or tuberculosis), and pituitary abscess. Sellar region tumors large enough to produce bitemporal hemianopsia almost always require evaluation by a neurosurgeon. Pituitary apoplexy is a rapidly developing, life-threatening syndrome discussed further in Chap. 19.

Homonymous Upper Quadrantanopsia

Lesions of the optic radiations within the temporal lobe (Meyer's loop) produce visual field loss in the contralateral superotemporal quadrant and the ipsilateral superonasal quadrant. The classic setting in which this occurs is following anterior

temporal lobectomy for refractory epilepsy. Other lesions in the temporal lobe which may produce homonymous upper quadrantanopsia include hemorrhages, arteriovenous malformations, and tumors. Any patient with this pattern of visual field deficits without a history of temporal lobectomy should undergo MRI of the brain with and without contrast to define the lesion.

Homonymous Hemianopsia

Posterior Cerebral Artery Infarction

Posterior cerebral artery (PCA) infarction is the most common cause of macular-sparing homonymous hemianopsia. Many patients with PCA infarctions do not recognize their deficits because central vision is spared or they may be able to compensate for their visual loss by simply moving their eyes. Some patients, however, note problems with reading or driving. Often, the deficits produced by PCA infarction that bring patients to clinical attention are confusional states or memory problems rather than visual field loss (Chaps. 1 and 21).

Alexia Without Agraphia

Alexia without agraphia results from a lesion (usually a PCA infarction) of the left occipital lobe and the splenium of the corpus callosum. Patients can write but cannot read – even something that they themselves have just written! The explanation for this syndrome is as follows:

- The left occipital lobe lesion produces a right homonymous hemianopsia. Thus, there is no perception of written material in the right half of space.
- The callosal lesion disconnects intact right visual cortex (that perceives written material in the left half of space) from the language centers in the left hemisphere.
- The ability to write is retained because the language centers in the left hemisphere are still connected to the motor centers in the left hemisphere that govern the physical act of writing.

Cortical Blindness

Bilateral Occipital Lobe Infarction

Bilateral PCA infarction leads to complete blindness. Because funduscopic examination and pupillary reactions are normal, a patient with cortical blindness may be diagnosed as a malingerer. This is especially true when cortical blindness occurs as part of Anton syndrome, in which the patient fabricates a detailed, often preposterous visual environment.

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is a severe encephalopathy produced by vasogenic edema and is discussed further in Chap. 1 [10]. In addition to encephalopathy, patients with PRES develop visual loss secondary to edema of the parietal and occipital lobes.

Functional Visual Loss

Visual loss secondary to malingering or conversion disorders may be difficult to diagnose with routine bedside examination. Patients with psychogenic visual loss frequently wear sunglasses indoors, modeling their "blind person behavior" on those of well-known blind celebrities such as Ray Charles and Stevie Wonder. Pupillary reactions and funduscopic examination are normal in patients with functional visual loss. Psychiatric disease may mimic any organic pattern of visual loss, but common patterns include tunnel vision, complete blindness, and subtle bilateral visual loss. In tunnel vision, visual field constriction is identical regardless of the distance from which the patient is examined: a patient with tunnel vision describes the same field defect at 1 foot as at 20 feet. Patients with functional complete blindness will not fall or injure themselves when attempting to traverse a path strewn with obstacles. Optokinetic drums or tapes may also be used to demonstrate preserved acuity in the patient who feigns blindness. The most difficult functional visual loss scenario to prove is the patient who complains of subtle bilateral visual loss. Diagnosing functional visual loss is often challenging, and formal ophthalmological evaluation is required in many cases.

Other Cortical Visual Syndromes

There are several visual processing disorders that do not cause frank visual loss but do cause problems with different visual modalities. These include:

Balint Syndrome

Balint syndrome consists of three core clinical features:

- Optic ataxia is the inability to reach for objects using visual guidance.
- Ocular apraxia is the inability to make directed eye movements towards a target of interest.
- Simultanagnosia is the inability to perceive the details of a complex visual scene, often tested at the bedside using a stimulus such as "The Cookie Theft" picture.

The lesions that produce Balint syndrome are in the bilateral occipitoparietal regions, classically infarctions in the watershed territories between the middle and posterior cerebral arteries.

Visual Object Agnosia

Visual object agnosia is an inability to identify an object using vision alone. It is divided into two forms:

Visual Apperceptive Agnosia

In this variant the patient cannot recognize a visually presented object at all, cannot match identical objects, and cannot copy an object with pencil and paper. Patients with visual apperceptive agnosia can recognize an object using the other senses: for example, a book might be recognized by its texture, weight, and smell. Cerebral lesions that produce visual apperceptive agnosia are typically diffuse, with carbon monoxide poisoning being a classical cause.

Visual Associative Agnosia

Similar to patients with visual apperceptive agnosia, patients with visual associative agnosia cannot recognize the visual form of an object. They can, however, match identical objects and draw pictures of objects presented to them. They cannot group similar objects (e.g., they cannot classify hand tools such as a screwdriver and a hammer as different from writing implements such as a pen or pencil.) Responsible lesions are in the occipital or parietal lobes.

Prosopagnosia

Patients with prosopagnosia do not recognize familiar faces, including those of family members. This syndrome is usually due to lesions of the right inferior occipitotemporal medial temporal (fusiform gyrus) region.

Cerebral Achromatopsia

The patient with cerebral achromatopsia cannot perceive colors. Deficits can range from a partial misidentification of two or more colors to a complete lack of color with the entire world appearing in shades of gray. Patients often have other visual deficits including visual field cuts or prosopagnosia. This syndrome is due to bilateral lesions in the lingual and fusiform gyri.

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Diplopia

6

Establishing Binocularity and Direction of Diplopia

Patients with a variety of neurologic, ophthalmologic, and psychiatric disorders complain of diplopia. The first step in diagnosing diplopia is to determine whether the problem occurs only when both eyes are viewing the target (binocular) or if it persists when one eye is closed (monocular). Binocular diplopia is usually secondary to nervous system dysfunction and therefore will be the focus of this chapter. Monocular diplopia is usually secondary to intraocular pathology and should prompt referral to an ophthalmologist. In some cases, monocular diplopia is due to psychogenic disease. Rarely, it may be due to central nervous system disease such as head trauma [1]. All patients with monocular diplopia also have binocular diplopia – monocular diplopia which disappears when both eyes are opened is always secondary to psychogenic disease. If it is not clear from the history whether diplopia is monocular or binocular, ask the patient to close or cover each eye in sequence. If the diplopia disappears when one eye is covered, it is binocular.

After establishing that diplopia is binocular, the next step is to determine whether it is horizontal, vertical, or mixed (diagonal or oblique). Ask the patient whether the images are stacked on top of each other, are side-by-side, or are diagonal to each other. For horizontal diplopia, it may be helpful to ask whether the images are worse at near (e.g., reading a book) or far (e.g., watching television). Horizontal diplopia worse with near viewing suggests an adduction deficit, while horizontal diplopia worse with distant viewing suggests an abduction deficit. For patients with vertical diplopia, ask about difficulty with reading or descending stairs, both of which suggest difficulty with depressing or intorting the eyes. It is also important to ask about fluctuating symptoms. Diplopia that changes from the horizontal to the vertical plane gets worse as the day progresses or that disappears and reappears later is suggestive of myasthenia gravis.

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Inspecting Ocular Misalignment

Inspecting the eyes before starting the formal examination often provides valuable information about ocular misalignment. In some cases, ocular misalignment is obvious at rest. For example, a severe oculomotor nerve lesion puts the eye in a "down and out" position due to the unopposed actions of the unaffected superior oblique and lateral rectus muscles. A severe abducens nerve lesion leads to medial deviation of the eye in the orbit. Shining a flashlight onto both eyes from a distance may uncover subtle diplopia: if the eyes are misaligned, light will reflect from different spots on the two eyes. Some patients who complain of diplopia have a head tilt indicating a torsional deficit, which is especially common in fourth nerve palsies.

Localizing the Dysfunctional Eye Movement

In order to localize the cause of binocular diplopia to a site in the nervous system, the dysfunctional eye movement must be identified. Figure 6.1 shows the two-step testing schematic for localizing horizontal diplopia, while Fig. 6.2 shows the three-step testing schematic for vertical diplopia. In most cases of dysfunction of a single eye movement, these rules are effective. This testing scheme may be less useful when multiple eye movements are abnormal or when the patient has a skew deviation.

- Step 1: Find the direction of maximal image separation. Ask the patient to follow your finger to the left, right, up, and down, observing for weakness of eye movements in each direction and inquiring specifically about worsening of double vision at each endpoint.

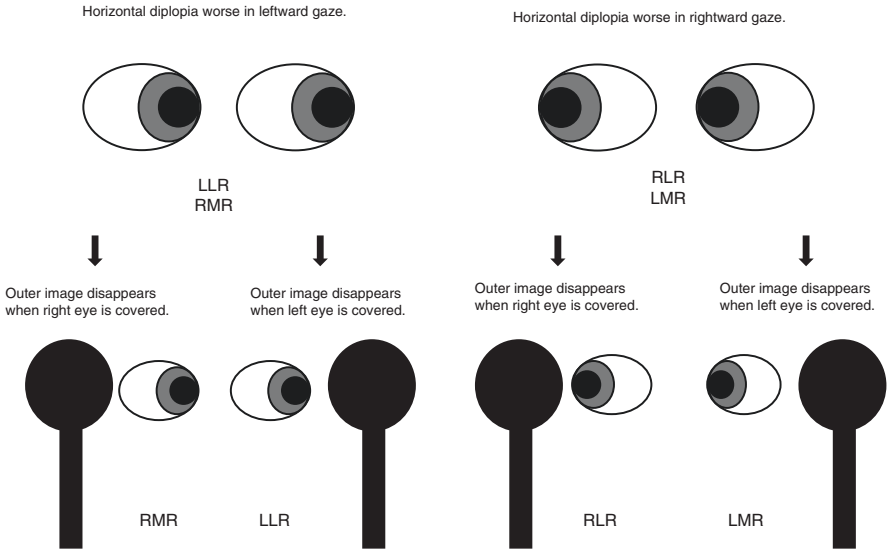

Fig. 6.1 Testing schematic for horizontal diplopia. *LLR* left lateral rectus, *LMR* left medial rectus, *RLR* right lateral rectus, *RMR* right medial rectus. See text for further details

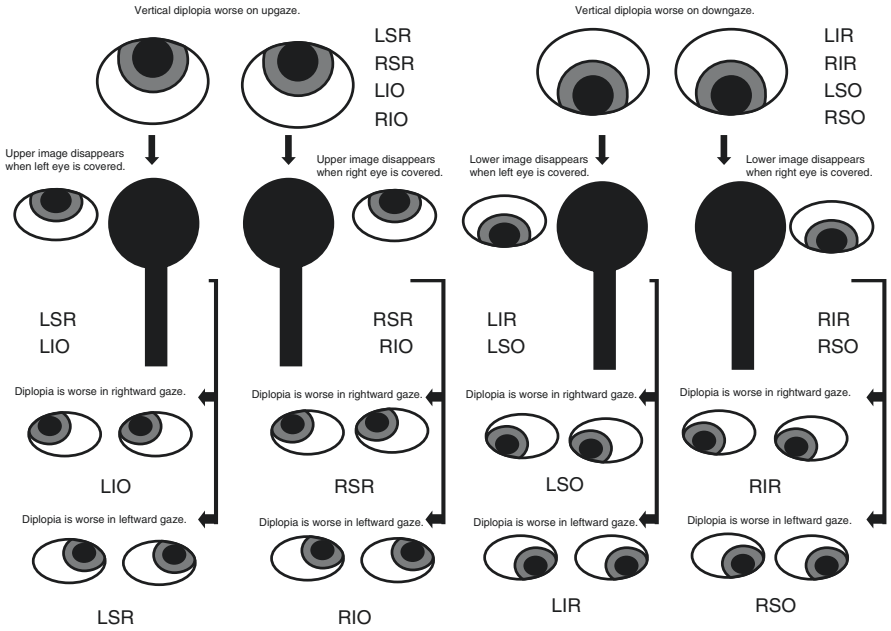

Fig. 6.2 Testing schematic for vertical diplopia. *LIO* left inferior oblique, *LIR* left inferior rectus, *LSO* left superior oblique, *LSR* left superior rectus, *RIO* right inferior oblique, *RIR* right inferior rectus, *RSO* right superior oblique, *RSR* right superior rectus. See text for further details

- Step 2: Determine which eye is seeing the false image. After the patient identifies the direction of maximal diplopia, point out to them that there is one image on the outside (e.g., to the right when looking to the right) and one image on the inside (e.g., to the left when looking to the right). Once they verify that there is an inner and an outer image, instruct them to cover one eye, and ask them which image disappears. The outer image will disappear when the abnormal eye is covered, i.e., *the eye that sees the false image will always see it as the outer one.* Steps 1 and 2 will localize the dysfunctional eye movement for patients with horizontal diplopia.
- Step 3, option 1 (for vertical diplopia): Steps 1 and 2 will localize the source of vertical diplopia to an oblique muscle or to a rectus muscle in one eye. The oblique muscles are the primary elevators and depressors of the eye in the adducted position, while the rectus muscles are the primary elevators and depressors of the eye in the abducted position. If vertical image separation is greater when the affected eye is adducted, then the oblique muscle is dysfunctional. If it is greater when the eye is abducted, then the rectus muscle is dysfunctional.
- Step 3, option 2 (not shown) (for vertical diplopia): Alternatively, the head tilt test can be performed by asking the patient to tilt their head to the side. The superior oblique and superior rectus are the main intorters of the eye, while the inferior oblique and inferior rectus are the main extorters of the eye. Therefore, if diplopia worsens when the head tilts to the left, the problem is in the left superior oblique, the left superior rectus, the right inferior oblique, or the right inferior rectus.

Localizations of Horizontal Diplopia

Abducens Nerve Palsy

Nuclear Lesions

The abducens nucleus, found in the pons, gives rise both to the abducens nerve which innervates the ipsilateral lateral rectus and to fibers which ascend in the medial longitudinal fasciculus (MLF) and synapse with the oculomotor nucleus, thereby yoking horizontal eye movements. Because lesions of the abducens nucleus affect fibers of both the abducens nerve and the MLF, lesions at this site lead to a gaze palsy towards the side of the lesion rather than simply restricting lateral movement of the ipsilateral eye. Nuclear lesions may also affect the facial nerve fascicles as they sweep around the abducens nucleus, leading to ipsilateral gaze palsy and ipsilateral facial paresis.

Fascicular Lesions

The abducens nerve fascicles project ventrally through the pons and cross the corticospinal tract. Lesions at this site, therefore, produce ipsilateral abducens nerve palsy and contralateral hemiparesis. The most common causes of abducens fascicle lesions are demyelination and ischemia.

Prepontine Segment Lesions

The abducens nerve emerges from the brainstem in the prepontine cistern and enters the cavernous sinus via Dorello's canal. The most important cause of abducens nerve palsy in the prepontine cistern is increased intracranial pressure, which often affects both abducens nerves simultaneously. In some cases, decreased intracranial pressure, as may occur after a lumbar puncture or as a consequence of spontaneous intracranial hypotension, may stretch the abducens nerve as it enters Dorello's canal. Gradenigo syndrome is characterized by ipsilateral facial pain and eye abduction weakness caused by simultaneous involvement of the fifth and sixth nerves at the tip of the petrous bone, usually by spread of infection from the inner ear.

Cavernous Sinus and Orbit Lesions

Within the cavernous sinus, the abducens nerve may be involved in isolation, although the other cranial nerves that travel through the cavernous sinus are often involved (see below). The abducens nerve emerges from the cavernous sinus, enters the orbit via the superior orbital fissure, and innervates the lateral rectus muscle. Important causes of abducens nerve lesions within the orbit include trauma, infection, and neoplasm.

Partial Oculomotor (Cranial Nerve III) Palsy

A more detailed discussion of the anatomy and pathology of the third nerve is provided below. Because the oculomotor nerve innervates four extraocular muscles, it does not usually lead to isolated eye adduction weakness.

Internuclear Ophthalmoplegia (INO)

INO is caused by a lesion of the medial longitudinal fasciculus (MLF), the pathway that connects the abducens nucleus to the contralateral oculomotor nucleus (Fig. 6.3). On examination, patients with INO cannot adduct the ipsilateral eye and have nystagmoid movements in the contralateral eye. Adduction is preserved with attempted convergence because the vergence centers in the midbrain adjacent to the oculomotor nuclei are preserved. The most subtle sign of INO is adduction lag, in which a slowed saccade is seen in the adducting eye. INO often occurs in combination with other ocular motor abnormalities including vertical nystagmus and skew deviation. Common causes of INO include multiple sclerosis, in which case the INO tends to be bilateral, and stroke, in which case the INO is more often unilateral.

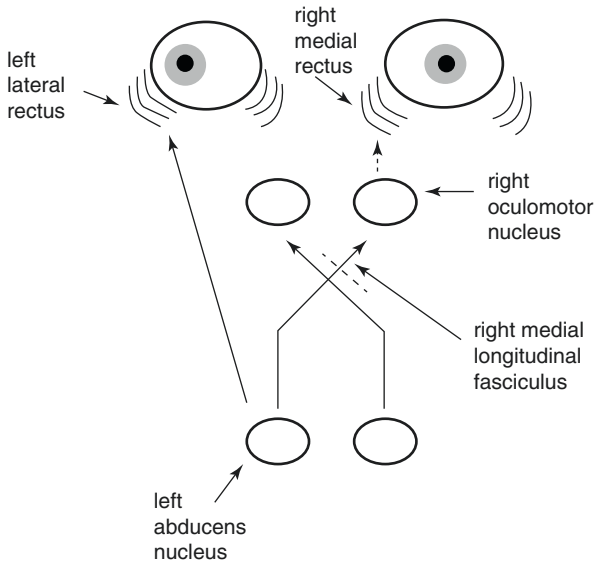

Fig. 6.3 Illustration of right internuclear ophthalmoplegia. A lesion of the right medial longitudinal fasciculus prevents adduction of the right eye. Abduction of the left eye is preserved

The term wall-eyed bilateral INO (WEBINO) refers to an inability of either eye to adduct.

The one-and-a-half syndrome is caused by a pontomesencephalic lesion of one abducens nucleus and both MLFs. The patient with a one-and-a-half syndrome is unable to abduct the eye ipsilateral to the lesion or to adduct either eye.

Duane Retraction Syndrome

Duane retraction syndrome is secondary to agenesis or hypoplasia of one or more ocular motor nuclei. The most common variant affects the abducens nucleus or nuclei, causing difficulty with abduction of the affected eye and retraction of the globe of the contralateral adducting eye. Variants exist in which adduction is impaired or both adduction and abduction are impaired. Because Duane syndrome does not usually produce diplopia, it is rare for an adult with this condition to require further evaluation or treatment. It is mentioned here because it may confuse the neuro-ophthalmologic assessment if it has not been identified previously.

Localizations of Vertical Diplopia

Trochlear Nerve Palsy

Trochlear nerve lesions produce vertical or oblique (diagonal) diplopia. The pattern of a trochlear nerve palsy is:

- Ipsilateral hypertropia (relative upward deviation of the ipsilateral eye)
- Worsening of the hypertropia when looking to the contralateral side (because the superior oblique is the main depressor of the adducted eye)
- Worsening of the hypertropia when tilting to the ipsilateral side (because the superior oblique is the main intorter of the eye)

One clue to the presence of trochlear nerve palsy is that the patient will tilt their head to the side opposite to the lesion in order to reduce their diplopia. Because the superior oblique is the main intorter of the eyeball, the hypertropic eye will be excyclotorted (externally rotated). Bilateral fourth nerve lesions can prove particularly challenging to diagnose, as they produce right hypertropia on left gaze and left hypertropia on right gaze.

Nuclear, Fascicular, and Cisternal Segment Lesions

The trochlear nucleus is found in the midbrain, *contralateral* to the superior oblique muscle which it innervates. Ischemic or demyelinating lesions may affect the nerve or its fascicles within the brainstem. Because of the proximity of the trochlear nucleus to the descending oculosympathetic fibers, nuclear lesions are often

accompanied by a Horner syndrome (Chap. 7) ipsilateral to the affected trochlear nucleus (i.e., affecting the eye contralateral to the affected superior oblique muscle). The fibers of the trochlear nerve decussate and emerge posteriorly from the midbrain. Along this segment, the trochlear nerve is most often affected by trauma. The trochlear nerve then runs anteriorly along the lateral aspect of the brainstem and enters the cavernous sinus.

Cavernous Sinus and Orbit Lesions

Lesions within the cavernous sinus (see below) are likely to affect the trochlear nerve in conjunction with other cranial nerves that pass through it. The trochlear nerve emerges through the superior orbital fissure to innervate the superior oblique muscle, which depresses and intorts the eye.

Skew Deviation

Skew deviation is vertical ocular misalignment produced by disruption of prenuclear vestibular inputs to the ocular motor nuclei. Discussing the neuroanatomy and physiology of skew deviation is beyond the scope of the text, and I will direct the interested reader to the review of Brodsky et al. [2]. Briefly, skew deviation should be considered as the cause of vertical diplopia under the following circumstances:

- When vertical diplopia is comitant (of the same magnitude) with both left and right gaze
- When exam suggests dysfunction isolated to the inferior rectus, superior rectus, or inferior oblique
- When internuclear ophthalmoplegia is present
- When the hypertropic (higher) eye is incyclotorted
- In patients with known brainstem disease

Lesions in a variety of locations within the brainstem, the cerebellum, and sometimes the peripheral vestibular system may lead to skew deviation. Approximately one third of patients with brainstem infarction will have skew deviation, and it often goes unrecognized or explained incorrectly as a “partial third nerve palsy” [3]. Other causes include hemorrhage, trauma, neoplasm, and demyelination.

Partial Third Nerve Palsy

Damage to the third nerve fibers that supply either the superior rectus or inferior oblique muscles without involvement of other structures innervated by the third nerve may produce vertical diplopia. The selective involvement of these specific muscles, however, is uncommon.

Localization of Multidirectional Diplopia

Oculomotor Nerve Palsy

Nuclear Lesions

The oculomotor nucleus consists of a cluster of subnuclei in the dorsal midbrain. The medial rectus, inferior rectus, and inferior oblique subnuclei are all ipsilateral to the muscles which they innervate. The superior rectus subnuclei are contralateral to the muscles which they innervate, while the levator palpebrae are innervated by a shared midline subnucleus. Thus, a lesion of one side of the oculomotor nuclear complex will affect the:

- Ipsilateral medial rectus
- Ipsilateral inferior rectus
- Ipsilateral inferior oblique
- Contralateral superior rectus
- Bilateral levator palpebrae

Pupilloconstrictor fibers are found in the Edinger-Westphal nucleus, as discussed in Chap. 7.

Fascicular Lesions

The oculomotor nerve arises from its nucleus in the midbrain and runs anteriorly in the brainstem as the oculomotor nerve fascicles. It contains fibers to the ipsilateral:

- Medial rectus, which adducts the eye
- Inferior rectus, which is the principal depressor of the abducted eye
- Inferior oblique, which is the principal elevator of the adducted eye and extorter of the eye
- Superior rectus, which is the principal elevator of the abducted eye
- Levator palpebrae, which is the principal elevator of the eyelid
- Pupilloconstrictor muscles

Fascicles of the third nerve run anteriorly in the midbrain, adjacent to several important structures (Fig. 6.4). A third nerve lesion which involves the adjacent red nucleus produces the Claude syndrome, characterized by oculomotor dysfunction and contralateral limb ataxia. More anteriorly within the midbrain, a lesion of the third nerve and cerebral peduncle produces the Weber syndrome, characterized by oculomotor dysfunction and contralateral hemiparesis.

Cisternal Segment Lesions

The third nerve emerges from the ventral midbrain in the interpeduncular cistern. It passes between the posterior cerebral and superior cerebellar arteries before

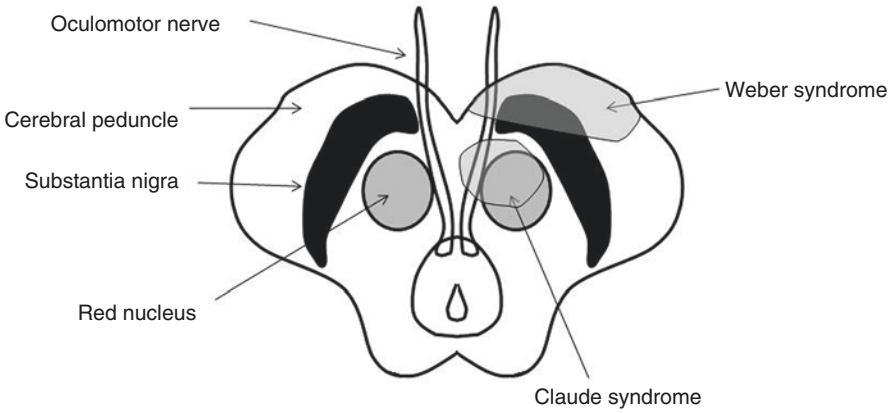

Fig. 6.4 Important lesions affecting the oculomotor nerve in the midbrain. Claude syndrome is characterized by an ipsilateral third nerve palsy and contralateral limb ataxia. Weber syndrome is characterized by an ipsilateral third nerve palsy and contralateral hemiparesis

penetrating the cavernous sinus. A mass lesion in the interpeduncular cistern affects the dorsally located pupilloconstrictor fibers first, leading to a dilated, unreactive pupil while sparing extraocular motor and lid levator fibers [4]. Complete palsy of the third nerve will develop if this mass lesion, most commonly an aneurysm of the posterior communicating artery or herniating uncus, is left untreated. Pupil-involving third nerve palsies are discussed in further details in Chap. 7.

Cavernous Sinus Lesions

The third nerve enters the cavernous sinus, where it is usually affected in combination with the other ocular motor nerves and the first two divisions of the trigeminal nerve. In the anterior cavernous sinus, the nerve divides into superior (which innervates the superior rectus and levator palpebrae) and inferior (which innervates the medial rectus, inferior rectus, inferior oblique, and pupilloconstrictors) divisions. Either division may be affected in isolation.

Ischemic Third Nerve Lesions

The typical clinical history of the ischemic third nerve lesion is that of an older patient with diabetes or other risk factors for vascular disease who develops the acute-to-subacute onset of retro-orbital pain and weakness of the extraocular muscles and the levator palpebrae. Pupil reactivity is usually spared because the superficial layer of the nerve which contains the pupillomotor fibers is relatively unaffected by ischemia. Pain often precedes the eye movement abnormalities by hours to days [5]. It is often called a “diabetic third” or an “ischemic third.” The precise localization of the pupil-sparing third nerve lesion is unclear and may lie within the midbrain fascicles or in the nerve proper after its emergence from the brainstem.

Wernicke Encephalopathy

Wernicke encephalopathy is the clinical triad of ataxia, ophthalmoplegia, and confusion in patients with thiamine deficiency, usually secondary to chronic alcohol use. Only a small minority of patients present with the complete triad, with confusion being the most consistent element [6]. Eye movement in any direction may be affected, although the sixth nerve is involved most frequently [7]. Treat patients with Wernicke encephalopathy with thiamine as described in Chap. 1. Timely and appropriate vitamin supplementation may reverse the ocular motor deficits within hours to days.

Cavernous Sinus Lesions

Deficits of multiple extraocular movements should always prompt consideration of cavernous sinus lesions, as the oculomotor, trochlear, and abducens nerves lie in proximity within the cavernous sinus. Other clues to a cavernous sinus lesion include ipsilateral facial and retro-orbital pain due to involvement of the first two divisions of the trigeminal nerve and visual field defects due to involvement of the adjacent optic chiasm (Chap. 5). The most serious cause of cavernous sinus syndrome is septic cavernous sinus thrombosis, a life-threatening emergency which must be treated quickly. Other symptoms include fever, proptosis, ptosis, and chemosis developing over hours to days. Patients usually have a preceding history of a sinus infection and may be immunocompromised. Untreated cavernous sinus thrombosis leads to blindness and clot propagation which may be fatal. Diagnosis of septic cavernous sinus thrombosis is confirmed with CT scan or MRV. A broad-spectrum antibiotic regimen, usually including vancomycin, metronidazole, and ceftriaxone should be administered. Controversy surrounds anticoagulation with heparin as an adjunct to antibiotics: it may prevent thrombus extension, promote recanalization, and reduce the risk of long-term complications, but high-quality data supporting its use are lacking [8]. Other important causes of cavernous sinus syndrome include noninfectious cavernous sinus thrombosis, aneurysmal rupture, and neoplasms.

Tolosa-Hunt Syndrome

Tolosa-Hunt syndrome is characterized by the acute-to-subacute development of painful ophthalmoplegia [9]. The first symptom is usually retro-orbital pain, followed several days later by ophthalmoplegia due to dysfunction of any of the ocular motor nerves. Ipsilateral facial pain, tingling, and numbness are secondary to involvement of the first and second divisions of the trigeminal nerve. Visual loss may occur as a result of optic nerve compression. As the symptoms suggest, Tolosa-Hunt syndrome is caused by a mass lesion within the cavernous sinus or the orbit.

Most commonly, this is an idiopathic granulomatous process, but the syndrome may also be caused by other pathologies including neoplasm, sarcoidosis, or tuberculosis. All patients require MRI of the orbit and cavernous sinus to try to identify a mass lesion. Symptoms of Tolosa-Hunt syndrome respond to steroids within 72 hours, but the response may be incomplete, and the symptoms may recur after steroid withdrawal. One of the challenges of Tolosa-Hunt syndrome is that both the idiopathic granulomatous form and most of the more dangerous processes which produce it are steroid-sensitive. Biopsy and resection of neoplastic or granulomatous masses may be considered with extreme caution in patients with disease that does not respond to steroids.

Orbital Lesions

Orbital lesions, usually secondary to trauma, neoplasm, or infection, may affect any of the extraocular muscles, either alone or in combination. These are usually evaluated and treated by ophthalmologists and therefore will not be discussed further.

Miller-Fisher Syndrome and Brainstem Encephalitis

The clinical triad of Miller-Fisher syndrome (MFS) is ataxia, ophthalmoplegia, and areflexia. It is often considered a variant of Guillain-Barre syndrome (Chap. 12), as it is also a subacutely progressive autoimmune demyelinating disorder that affects the peripheral nervous system. MFS also overlaps with Bickerstaff brainstem encephalitis, a disorder characterized by ophthalmoplegia, ataxia, and signs of central nervous system dysfunction including encephalopathy and hyperreflexia. GQ1b antigens are found in the ocular motor nuclei, in the muscle spindles of the limbs, and likely in the reticular formation of the brainstem [10]. The diagnosis of MFS is confirmed by finding GQ1b antibodies in the serum. MRI is usually normal. There is no consensus as to the best treatment of MFS. It is usually self-limited, but for patients with severe symptoms, a trial of intravenous immunoglobulin or plasmapheresis (using protocols similar to those used for Guillain-Barre syndrome) may be warranted. In general, ataxia improves before ophthalmoplegia [11].

Cranial Polyneuropathy

A small number of conditions may affect multiple cranial nerves simultaneously. These are generally associated with meningeal inflammation (“basilar meningitis”) and include carcinomatous meningitis, bacterial meningitis, tuberculosis, sarcoidosis, and Lyme disease. Contrast-enhanced MRI of the brainstem and lumbar puncture are indicated to evaluate patients with cranial polyneuropathy.

Restrictive Disorders

Restrictive extraocular muscle disease prevents movement of the eye in the direction of the involved extraocular muscle. For example, restriction of the medial rectus keeps the eye in the adducted position and therefore resembles an abduction deficit. The most common causes of restrictive ophthalmopathy are Graves disease, which usually affects the inferior and medial recti, and connective tissue disorders. Restrictive disorders are diagnosed by the forced duction test, in which an ophthalmologist demonstrates restricted movement of the anesthetized globe when attempting to move the eyeball with a pair of forceps.

Convergence Insufficiency

Convergence insufficiency is characterized by binocular horizontal diplopia, excessive exodeviation, and eye strain with near fixation. Blurring often occurs after reading for a few minutes, and headaches are common. College students who are doing unaccustomed amounts of reading and older patients with new bifocal or progressive lens prescriptions are two populations at risk for convergence insufficiency. Eye exercises to reduce convergence insufficiency are often successful at relieving symptoms.

Spasm of the Near Reflex

Spasm of the near reflex is characterized by painful attacks of bilateral convergence, accommodation, and miosis [12]. It might be confused with sixth nerve palsy because abduction of the eyes is impaired. The diagnosis is established by demonstrating miosis on attempted lateral gaze. Spasm of the near reflex is usually a functional (psychogenic) disorder, does not require further investigation, and is treated by counseling and reassurance.

Fluctuating Diplopia-Ocular Myasthenia Gravis

Myasthenia gravis is a disorder of postsynaptic neuromuscular function discussed further in Chap. 10. Ocular myasthenia gravis is characterized by diplopia and ptosis without proximal muscle weakness. Patients with ocular myasthenia classically report that their diplopia is fatigable, initially appearing after reading or looking at a computer screen or towards the end of the day. The fluctuating examination in myasthenia gravis is almost diagnostic, with diplopia localizing to different muscles at different times. For example, in the morning, the patient may have diplopia which localizes to the left inferior oblique, while in the afternoon the diplopia localizes to the right medial rectus. Fixed, nonfatigable diplopia that persists is less characteristic of myasthenia gravis but does not exclude the diagnosis.

To demonstrate fatigability, ask the patient to look upwards for 1–2 minutes, and observe for worsening diplopia or visible ocular deviation. Two provocative tests may help to establish fatigability, and therefore, a diagnosis of ocular myasthenia gravis:

- The ice test requires a patient with active diplopia or ptosis. Instruct the patient to close the affected eye, and place a plastic bag filled with ice over that eyelid for 1–2 minutes. An improvement in diplopia or ptosis immediately after the ice is removed is often clearly visible and suggestive of myasthenia gravis.
- The edrophonium (Tensilon) test is most useful in patients with active diplopia or ptosis. Edrophonium is a short-acting acetylcholinesterase inhibitor which is given intravenously. Because edrophonium may cause bradycardia, the patient should be placed on cardiac telemetry, and atropine should be available at the bedside. First, inject a 2 mg test dose of edrophonium over 1 minute to assure that the patient tolerates it. Next, inject an 8 mg dose of edrophonium over 2 minutes, and observe for an improvement in ptosis or diplopia. Should the patient become bradycardic, inject atropine (0.5 mg × 1, up to a total dose of 3 mg), and continue cardiac telemetry for at least 30 minutes (by which point all the edrophonium will be metabolized). It is usually best to perform the edrophonium test with the assistance of a blinded observer. True blinding of an observer may be challenging, however, as side effects of edrophonium including lacrimation and rhinorrhea are often obvious.

Diagnostic testing for myasthenia gravis is discussed further in Chap. 10. It is important to note that only half of patients with ocular myasthenia will have antibodies to the acetylcholine receptor.

I attempt to treat most ocular myasthenics with the acetylcholinesterase inhibitor pyridostigmine at a dose of 30–60 mg tid-qid. Side effects include gastrointestinal cramping, lacrimation, and rhinorrhea. There is little benefit to increasing the total daily dose of pyridostigmine beyond 240 mg. If disabling ocular symptoms persist after more than a week of pyridostigmine treatment, then consider initiating corticosteroids as outlined in Chap. 10.

Diagnostic Testing

Unless there is obvious evidence for myasthenia gravis, almost all patients with diplopia of neurologic origin require a brain imaging study, usually MRI with diffusion-weighted imaging and contrast. Thin cuts through the brainstem, cavernous sinus, and orbits should be performed as indicated by the history and physical examination. These studies may be normal, however, when small, isolated nuclear or brainstem fascicular lesions are present. Vascular imaging is necessary in patients with suspected aneurysms. Lumbar puncture is useful when infectious, inflammatory, or neoplastic disorders are suspected.

Treatment

Treating the underlying disorder offers the best chance of reversing diplopia. Many patients start to wear an eye patch (sometimes over the paretic eye if that one has poorer acuity at baseline) before even seeing a doctor. Patches may be helpful for diplopia of short duration. Most patients with chronic, fixed diplopia without a reversible underlying cause require referral to an ophthalmologist for consideration of prisms or, in some cases, corrective surgery.

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Disorders of the Eyelids and Pupils

7

Ptosis and Lid Retraction

Drooping eyelids may come to clinical attention independently but are more often part of a larger neurologic syndrome. Understanding potential lesion sites is essential to localizing the source of the problem correctly (Fig. 7.1).

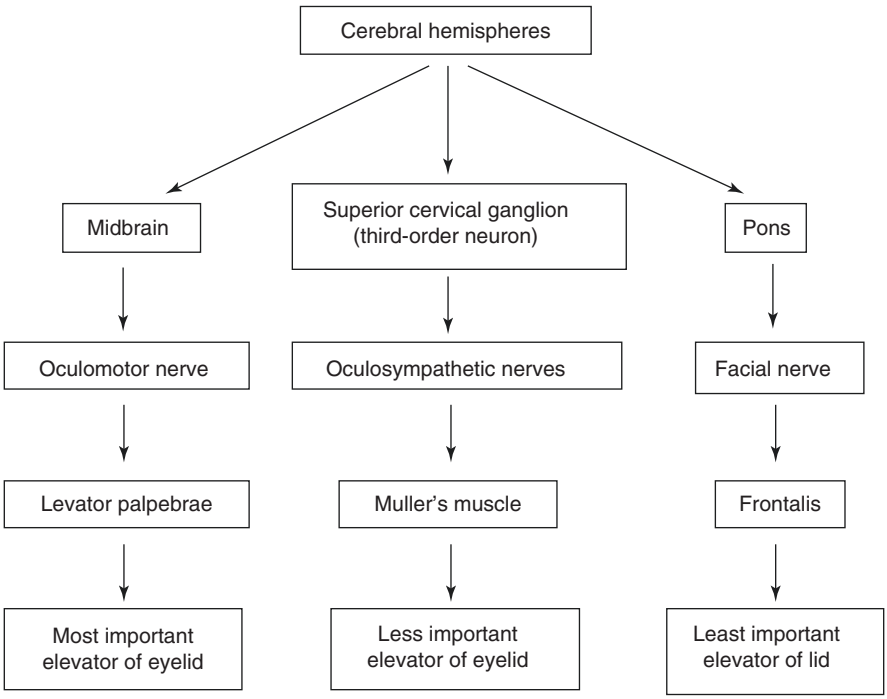

Fig. 7.1 Schematic of the three pathways which control elevation of the eyelids

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Supranuclear Lesions

Hemispheric strokes or other large hemispheric lesions may lead to contralateral, or in some cases bilateral, ptosis [1]. Because these lesions are generally large and produce hemiparesis and disorders of consciousness among other neurologic symptoms, ptosis may go unrecognized.

Nerve Lesions

Oculomotor Nerve

The oculomotor nerve innervates levator palpebrae, the main elevator of the lid. The Edinger-Westphal subnuclei which control eyelid elevation are located within a shared midline complex in the midbrain. Oculomotor nuclear lesions, therefore, produce bilateral ptosis. Lesions of the oculomotor nerve proper cause ptosis in combination with extraocular muscle dysfunction, as described in Chap. 6. Lesions within the anterior cavernous sinus or orbit may involve only the superior division of the oculomotor nerve, producing deficits restricted to levator palpebrae and superior rectus.

Oculosympathetic Nerves

The oculosympathetic nerves innervate Muller's muscle, a minor elevator of the lid (see Fig. 7.2 and "Anisocoria"). Ptosis which arises from oculosympathetic dysfunction, therefore, is milder than ptosis due to oculomotor nerve dysfunction.

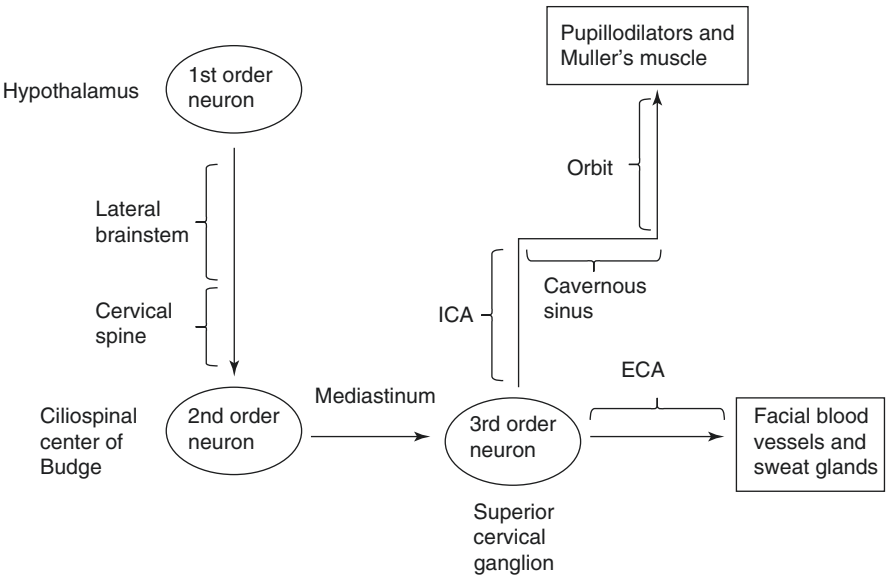

Fig. 7.2 Schematic of the oculosympathetic pathway. Lesions of this pathway result in Horner syndrome

Unlike oculomotor nerve dysfunction, however, a lesion of the oculosympathetic pathway may produce ptosis as the most prominent finding (i.e., a partial Horner syndrome). Oculosympathetic dysfunction may also lead to inverted ptosis in which the lower eyelid is slightly elevated compared to its expected anatomic position.

Facial Nerve

The facial nerve innervates frontalis, the least important of the lid elevators: dysfunction of the facial nerve usually does not lead to clinically important ptosis.

Neuromuscular Junction Lesions

Myasthenia gravis is the most important cause of ptosis localized to the neuromuscular junction. The distinguishing feature of ptosis in myasthenia gravis is that it tends to fluctuate over time or to worsen towards the end of the day. Ptosis is common in patients with both ocular and generalized myasthenia gravis (Chaps. 6 and 10). Besides showing fatigue upon sustained upgaze, a patient with myasthenia gravis may also demonstrate a "peek sign" which can help distinguish it from other forms of ptosis: when the patient is asked to sustain eye closure, the orbicularis oculi will fatigue, revealing a sliver of sclera.

Botulism is the other neuromuscular junction disorder that may lead to ptosis (Chap. 12). Ptosis in foodborne and wound botulism is followed quickly and overshadowed by bulbar dysfunction and generalized weakness. Iatrogenic botulism, however, may lead to isolated ptosis: patients who receive botulinum toxin injections in the forehead or around the eyes for cosmetic purposes, headaches, or blepharospasm may develop symptoms several hours to days after the injection as the toxin diffuses into the levator palpebrae or Muller's muscle. Because many patients do not spontaneously reveal that they are receiving botulinum toxin injections, it is important to ask about exposure in patients with undiagnosed ptosis.

Muscle Lesions

Ptosis secondary to myopathy is usually bilateral, symmetric, and fixed. Oculopharyngeal muscular dystrophy (OPMD) is inherited in an autosomal dominant fashion, begins in adulthood, and may be associated with other signs of extraocular muscle dysfunction and swallowing dysfunction (Chap. 8). Chronic progressive external ophthalmoplegia (CPEO) is a mitochondrial myopathy which also produces fixed bilateral ptosis. Patients with CPEO have accompanying weakness of eye movement, but rarely complain of diplopia.

Soft Tissue Lesions

When focusing on the nervous system exclusively, it is easy to overlook non-neurologic causes of ptosis. Soft tissue problems are often responsible for isolated

ptosis. Degeneration of the aponeurosis of the levator palpebrae is common in older patients but may also occur as a result of trauma. It is often difficult to tease apart from myasthenic ptosis, as it tends to worsen towards the end of the day. Clues to the diagnosis include thinning of the skin above the tarsal plate and the presence of normal lid excursion with maximal effort [2].

Dermatochalasis is also a disorder of older patients and results from drooping of redundant skin and other soft tissue over the eyes. Peeling back this excess skin reveals that eyelid function is normal.

Lid Retraction

In some cases, the eye with the widened palpebral fissure is the abnormal one because the eyelid is retracted. Lid retraction may be unilateral, as in Bell's palsy or bilateral, as in Graves' disease or the dorsal midbrain (Parinaud) syndrome.

Treatment of Ptosis and Lid Retraction

Many patients with ptosis and lid retraction have mild symptoms that do not necessarily require treatment. Some causes, such as myasthenia gravis, Bell's palsy, and Graves' disease respond to the treatment of the underlying disorder. Others such as iatrogenic botulism resolve over time. Patients with disabling, irreversible ptosis may require referral to an oculoplastic surgeon for consideration of eyelid crutches or lid surgery.

Other Disorders of the Eyelids

Blepharospasm

Blepharospasm is a focal dystonia characterized by intermittent sustained contraction of the orbicularis oculi muscles resulting in tight eye closure. Although it may affect only one eye at onset, almost all patients eventually develop bilateral symptoms [3]. Blepharospasm may be a mild problem or may be severe and frequent enough to cause functional blindness. Eye strain tends to worsen symptoms, and similar to other dystonias (Chap. 14), blepharospasm may improve with sensory tricks such as gently stroking the eyelids or forehead. When blepharospasm is associated with oromandibular dystonia, it is known as Meige syndrome. In most cases, blepharospasm is an idiopathic condition, but it may also be associated with Parkinson disease, other extrapyramidal disorders, or neuroleptic exposure. Blepharospasm responds best to local treatment with botulinum toxin injections. Anticholinergic agents such as trihexyphenidyl and dopaminergic agents including levodopa are only modestly effective.

Eyelid-Opening Apraxia

Eyelid-opening apraxia is a disorder defined by the combination of [4]:

- Inability to open the eyes
- Excessive frontalis contraction during attempted eyelid opening
- No evidence of orbicularis oculi contraction to suggest blepharospasm
- No evidence of oculomotor or oculosympathetic dysfunction
- No evidence of ocular myopathy

It may be present in isolation, but is often associated with an extrapyramidal disorder, particularly progressive supranuclear palsy and Parkinson disease. Symptomatic improvement with levodopa or focal botulinum toxin injection is typically modest [5].

Anisocoria

With the possible exception of mild photophobia produced by an abnormally dilated pupil, isolated anisocoria is unlikely to cause bothersome symptoms. However, it is associated with ominous processes such as posterior communicating artery aneurysm and uncal herniation and often leads to urgent neurological consultation when identified on examination. Not all anisocoria is acquired: if old photographs of the patient are available, examine them carefully to determine if the anisocoria is longstanding or more recent in onset. An important but infrequent sign of chronic developmental anisocoria is hypochromia iridis, a bluish or grayish discoloration of the iris associated with a small pupil.

The first step in determining the source of anisocoria is figuring out which pupil is abnormal: the big one (mydriasis) or the small one (miosis). This is accomplished by examining the pupils in light and dark. Anisocoria that is worse in light points to failure of the large pupil to constrict and to a problem with the parasympathetic system. Anisocoria that is worse in dark points to a failure of the smaller pupil to dilate and, therefore, to a problem with the sympathetic system.

Anisocoria Worse in Light (Parasympathetic Dysfunction)

Nuclear Lesions

The paired Edinger-Westphal nuclei lie in the oculomotor complex of the midbrain and give rise to pupilloconstricting fibers. Because lesions of the Edinger-Westphal nuclei are bilateral, they should cause symmetric pupillary dilation and should not lead to anisocoria.

Fascicular and Subarachnoid Lesions

The pupilloconstrictor fibers travel anteriorly through the midbrain with the fascicles of the oculomotor nerve. Fascicular lesions, therefore, produce pupillary dilation accompanied by extraocular muscle weakness (Chap. 6). As they emerge from the anterior aspect of the midbrain in the interpeduncular fossa, the superficial pupilloconstricting fibers of the third nerve are susceptible to compression by structural lesions. The two most important of these are expanding aneurysms of the posterior communicating artery (PCOM) and the herniating uncus of the temporal lobe, both of which are neurologic emergencies that require urgent neuroimaging and management. Although anisocoria secondary to a PCOM aneurysm may be isolated, anisocoria secondary to uncal herniation will be accompanied by altered mental status, coma, and other focal neurologic findings (Chap. 1).

Cavernous Sinus Lesions

The pupilloconstricting fibers in the oculomotor nerve course through the cavernous sinus (Chap. 6). Adjacent structures include the trochlear, ophthalmic, maxillary, and abducens nerves. Thus, isolated anisocoria is unlikely in cavernous sinus lesions.

Ciliary Ganglion Lesions

The oculoparasympathetic fibers pass through the ciliary ganglion within the orbit. Lesions at this site result in a large, dilated, unreactive pupil. The classical ciliary ganglion lesion is an Adie tonic pupil, an idiopathic condition which is most common in young and middle-aged women. Adie tonic pupil is diagnosed by finding denervation supersensitivity of the pupilloconstricting fibers: a dilute (0.1%) solution of the cholinergic agent pilocarpine causes brisk pupilloconstriction.

Iris Lesions

The pupilloconstricting fibers in the iris are susceptible to damage during eye surgery or other orbital trauma. The oculoparasympathetic fibers may also be blocked by anticholinergic medications such as atropine or scopolamine that are placed into the eye intentionally by malingerers or splashed into the eye accidentally. The key finding of a pharmacologically dilated pupil is that it will not constrict, even in response to concentrated (1%) pilocarpine.

Unlocalized Lesions

Benign episodic unilateral mydriasis is a migraine-associated phenomenon that is a diagnosis of exclusion [6].

Clinical Approach

The first step in evaluating oculoparasympathetic dysfunction is to perform a thorough history and neurologic examination to define dysfunction of adjacent structures and investigate for a history of eye surgery or trauma. It is especially important to exclude the possibility of a compressive lesion of the third nerve – because an aneurysm of the posterior communicating artery cannot be missed, consider an

MRA, CTA, or even a conventional angiogram in all patients with isolated oculoparasympathetic dysfunction.

In patients with isolated pupilloconstriction defects that remain undiagnosed after history, physical examination, and investigation for dangerous etiologies, use dilute pilocarpine drops to investigate for the possibility of an Adie tonic pupil. If denervation supersensitivity is absent, then use concentrated pilocarpine drops to investigate for pharmacologic blockade.

Oculoparasympathetic dysfunction which remains undiagnosed after comprehensive examination may require referral to an ophthalmologist.

Anisocoria Worse in Dark (Sympathetic Dysfunction)

Damage to the oculosympathetic pathway is known as Horner syndrome and, when complete, is characterized by ipsilateral miosis, ptosis, and facial anhidrosis. The oculosympathetic fibers travel in a three-neuron pathway (Fig. 7.2):

First-Order Neuron

The first-order neuron is found in the hypothalamus. Its axons descend through the lateral brainstem and cervical spinal cord. Anisocoria is unlikely to be the most prominent result of a lateral brainstem lesion, as nearby structures are also likely to be affected, producing a Wallenberg syndrome (Chap. 21). Spinal cord lesions are similarly unlikely to produce anisocoria as the major complaint.

Second-Order Neuron

The first synapse in the oculosympathetic pathway occurs at the C8–T1 level of the spinal cord in the ciliospinal center of Budge. Axons which arise from the second-order neuron pass through the mediastinum, superior to the apex of the lung and inferior to the subclavian artery. This is a common site for the oculosympathetic tract to be compressed by an apical lung cancer (Pancoast tumor), sometimes in association with a painful ipsilateral brachial plexopathy (Chap. 16). The second-order neuron is also vulnerable to injury from attempted subclavian venous catheter placement.

Third-Order Neuron

The axons of the second-order neuron synapse in the superior cervical ganglion. Axons to the eyelid and pupil travel with the internal carotid artery, while those that control facial perspiration follow the external carotid artery. Lesions of the third-order neuron, therefore, do not produce facial anhidrosis. Intracranial oculosympathetic fibers travel with the ophthalmic nerve through the cavernous sinus and into the orbit with the long ciliary nerves to reach the pupillodilators. Carotid artery dissection is the most serious cause of a Horner syndrome affecting the third-order neuron and is associated with severe ipsilateral headache and facial pain (Chap. 19). Cluster headache and the indomethacin-responsive headaches may produce similar symptoms.

Clinical Approach

The history, examination, and neighborhood signs of nervous system dysfunction help with the selection of radiologic studies in evaluating Horner syndrome:

- Wallenberg syndrome in a patient with a lateral brainstem lesion
- Painful ipsilateral brachial plexopathy in a patient with a Pancoast tumor
- Ipsilateral headache in a patient with carotid artery dissection
- Ipsilateral ocular motor abnormalities in a patient with a cavernous sinus lesion

Patients in whom none of these signs is present require a broader selection of imaging studies to help localize the dysfunction, including MRI of the brain (paying particular attention to the lateral brainstem and cavernous sinus), MR or CT angiography of the cervical vessels, and CT scan of the chest. Although eye drops containing cocaine and hydroxyamphetamine help to localize the site of Horner syndrome, their use has been supplanted largely by imaging studies, which are more readily available in emergency settings.

Physiologic Anisocoria

Anisocoria of up to 1 mm, usually worse in dark, may be observed in the absence of any recognizable sympathetic or parasympathetic pathology. Physiologic anisocoria is usually long-standing and is best diagnosed by examining old photographs. In many cases, however, it remains a diagnosis of exclusion, and careful evaluation for other sources of anisocoria must be conducted first.

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Facial Weakness, Dysarthria, and Dysphagia

8

Lower Brainstem Symptoms

While it may seem that the complaints included within this chapter resemble a hodgepodge of problems not addressed elsewhere in this text, the unifying feature of facial movement, speech, and swallowing is that the lower motor neurons that control them all lie within the pons and medulla. Because these motor neurons occupy a small volume within the brainstem, a tiny focus of ischemia, inflammation, or neoplasia often leads to simultaneous facial weakness, dysarthria, and dysphagia.

Facial Weakness

Anatomy

Figures 8.1 and 8.2 are rough schematics of the innervation of the muscles of facial expression and associated structures. Fibers derived from the motor cortex descend through the corona radiata, the internal capsule, and the cerebral peduncle to reach the contralateral facial nucleus. Most of the fibers from the lower 1/3 of the motor cortex project to neurons within the contralateral facial nucleus, while direct cortical projections to the components of the facial nucleus that control the upper part of the face are less robust [1]. The facial nerve fascicles travel medially and posteriorly through the pons, curving around the abducens nucleus. They then turn laterally to emerge from the ventrolateral pons as the facial nerve. The nerve courses through the cerebellopontine angle and enters the internal auditory meatus. In both locations, the facial nerve lies in proximity to the vestibulocochlear nerve. The facial nerve then passes from the internal auditory meatus into the facial canal. There are two clinically important branches that arise from the nerve within the facial canal:

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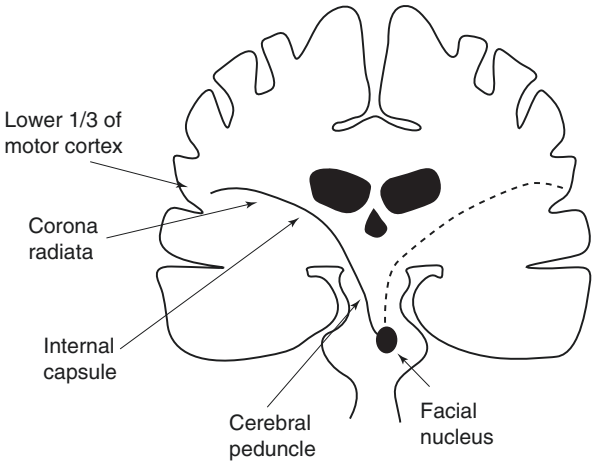

Fig. 8.1 Schematic showing upper motor neuron control of facial movement. The section of the facial nucleus which innervates the lower half of the face receives predominantly contralateral (solid line) but also some ipsilateral (dashed line) innervation from the lower 1/3 of the motor cortex. The section of the facial nucleus which innervates the upper half of the face receives little cortical input

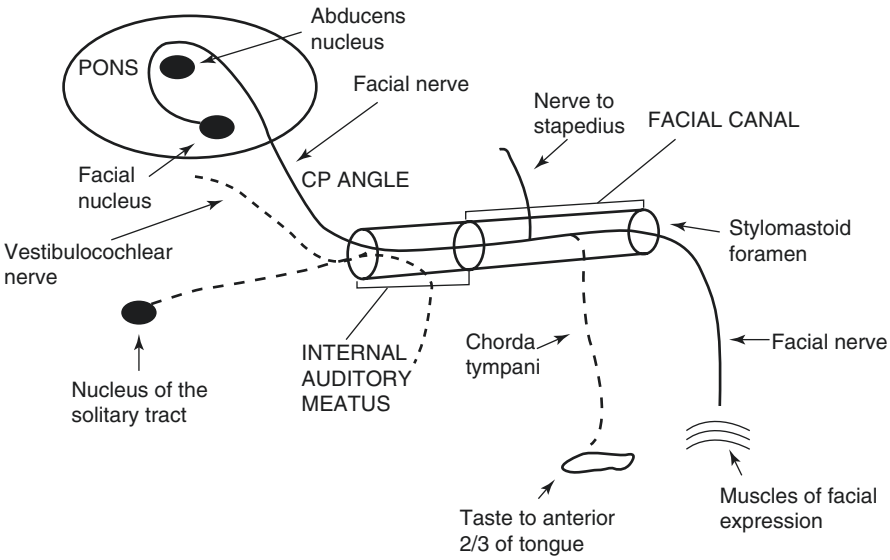

Fig. 8.2 Simplified schematic of the facial nerve. See text for details

the nerve to stapedius which helps to dampen the vibration of the stapes and the chorda tympani which contains taste fibers from the anterior 2/3 of the tongue. The neurons for these taste fibers are found in the nucleus of the solitary tract and not the facial nucleus. The facial nerve emerges from the facial canal via the stylomastoid foramen to innervate the muscles of facial expression.

Examination of Facial Movement

Comprehensive neurologic examination of the four clinically important functions of the facial nerve helps to determine the site of the lesion:

1. Examine the upper half of the face by asking the patient to lift their eyebrows, wrinkle their forehead, and close their eyes tightly. In patients with severe upper facial weakness, the sclera will be visible when the patient attempts to close the eye (the Bell phenomenon).
2. Examine the lower half of the face by asking the patient to show their teeth and hold air in their cheeks.
3. Although stapedius cannot be tested at the bedside, ask the patient whether loud or high-pitched noises are particularly irritating.
4. Finally, check taste on the anterior 2/3 of the tongue by using a sweetened fruit drink. This works much more effectively than using sugar. Pipette a very small volume of the fruit drink into a straw and have the patient close their eyes. Place one drop on the affected side of the tongue first, and ask the patient whether they taste the sweetness. It is important that the patient keep their mouth open during this test to prevent spread of the fruit drink to the other side of the tongue or to the taste buds on the posterior 1/3 of the tongue or pharynx. If the patient does not taste anything on the affected side, place one drop of fruit drink on the normal side of the tongue to verify that taste is intact on that side.

Differentiating Between Central and Peripheral Facial Weakness

Acute-onset, unilateral facial weakness is a common problem leading to neurologic consultation. The question of interest to the referring physician is whether the facial weakness is due to a stroke and requires inpatient evaluation or to Bell's palsy and may be managed on an outpatient basis. For clinical purposes, the most reliable way to differentiate between central and peripheral lesions is by examining the upper half of the face: cortical lesions do not tend to affect the upper half of the face, as the motor neurons that innervate the upper half of the face receive scant cortical input. Keep in mind, however, that a stroke within the pons (a lesion of the central nervous system that affects the facial nerve fascicles) may produce facial weakness that appears to be peripheral in origin. The following neighborhood signs and symptoms help to localize the problem in difficult cases:

1. Hand weakness ipsilateral to facial weakness strongly suggests pathology involving the contralateral motor cortex, as the face and hand areas are adjacent to each other on the motor homunculus.
2. Paralysis of ipsilateral conjugate gaze or of ipsilateral eye abduction places the lesion in the pons where the facial nerve fascicles cross the abducens nucleus and nerve.

3. The combination of facial weakness and dysphagia points to a lesion involving both the pons and medulla or the lower cranial nerves.
4. Ipsilateral hearing loss points to a lesion involving the facial nerve in combination with the vestibulocochlear nerve in the cerebellopontine angle (Chap. 23) or internal auditory meatus.
5. Ipsilateral hyperacusis (intolerance of high-pitched sounds) accompanies facial nerve lesions proximal to the departure of the nerve to stapedius, provided that the vestibulocochlear nerve is spared.
6. Loss of taste from the anterior 2/3 of the tongue accompanies lesions within the cerebellopontine angle, internal auditory meatus, or facial canal proximal to the takeoff of the chorda tympani.
7. Isolated weakness of the muscles of facial expression of both the upper and lower halves of the face points to a lesion of the nerve in the facial canal distal to the takeoff of the chorda tympani.

Causes of Facial Weakness

Supranuclear Lesions

The upper half of the face should be spared in a supranuclear lesion. Cortical lesions, because of the organization of the motor homunculus, usually produce contralateral facial weakness accompanied by hand weakness. Lesions within the corona radiata or internal capsule also produce arm weakness or arm and leg weakness. Strokes are the most common causes of supranuclear facial weakness.

Pontine Lesions

Pontine lesions (most commonly strokes, tumors, or demyelinating diseases) cause flaccid facial palsy that mimics Bell's palsy. Although the lesion is in the brainstem, it is technically a lower motor neuron lesion because the fascicles of the nerve rather than the facial nucleus itself are involved. As noted above, the facial nerve fascicles first run in proximity to the abducens nucleus and then the corticospinal tract. Clues that suggest a pontine lesion, therefore, include deviation of the eyes to the opposite side, ipsilateral lateral rectus palsy, or contralateral hemiparesis. Because the fascicles of the facial nerve in the pons do not contain taste fibers (which run in the chorda tympani), finding preserved taste in patients with fascicular lesions and impaired taste in those with peripheral lesions is useful in differentiating between the two lesion sites.

Bell's Palsy and Facial Nerve Lesions

Bell's palsy is considered an idiopathic disease, though most cases are likely caused by active or reactivated herpes zoster or herpes simplex viral infections of the facial nerve within the geniculate ganglion. A patient with Bell's palsy may note difficulty with closing their eye, slurring of their speech, or losing food from the corner of

their mouth that develops over the course or hours to days. They may also note reduced taste or feel that loud noises are particularly intense, though these are not usually uncovered unless sought specifically while taking the history. Although they may report that their face feels numb, this abnormal sensation is caused by difficulty moving the face rather than by specific involvement of sensory fibers in the trigeminal nerve. Indicators of "symptomatic" rather than idiopathic peripheral facial nerve palsy include headache, fever, involvement of other cranial nerves, and bilateral facial palsy. These features should prompt investigation for Lyme disease, sarcoidosis, HIV, and Sjogren syndrome.

Treatment options to accelerate the improvement of Bell's palsy include steroids and antiviral agents. The largest controlled studies suggest that steroids increase the likelihood of recovery in patients with Bell's palsy and that the addition of an antiviral agent does not offer an additional benefit [2, 3]. Smaller studies, however, support the addition of an antiviral agent for patients with more severe deficits [4]. For most patients, starting prednisone 60–80 mg qd within 3–7 days of onset is the most appropriate treatment. A 1-week course of acyclovir 1000 mg tid may be added to the prednisone for patients with severe palsies. Provide artificial tears and an eye patch to prevent corneal abrasions for patients who have difficulty with closing their eye. The prognosis of Bell's palsy depends on the initial degree of deficits: approximately 60% of patients with complete paralysis make a full recovery, compared to 95% with incomplete paralysis at diagnosis [5]. Younger patients and those whose recovery begins within 3 weeks of onset have better outcomes.

Incidental Facial Weakness

Incidental mild facial asymmetry is a frequent finding on neurologic examination. The question arises as to whether this facial weakness is a component of the process that brings the patient to neurologic attention (especially relevant in patients with suspected multifocal disease such as multiple sclerosis) or whether it is a preexisting, incidental finding. Asking the patient or available family member whether the facial weakness is old may help in some cases. Examining old pictures of a patient (frequently available on their driver's license or cell phone) is another option. Examining for synkinesis may also be helpful: axon sprouts that form during healing of facial nerve injuries often innervate both orbicularis oculi and orbicularis oris, so that when a patient with an old facial nerve palsy blinks, the ipsilateral corner of the mouth rises.

Dysarthria

Dysarthria is defined as a disorder of the mechanical production of speech. Although it is distinct from aphasia, it accompanies nonfluent aphasias in many cases (Chap. 3). The following are the most important subtypes of dysarthria [6]:

Spastic (Upper Motor Neuron) Dysarthria

The upper motor neurons for speech are found in the mouth area of the motor cortex in the precentral gyrus. Fibers descend through the subcortical white matter and internal capsule to reach the lower motor neurons in the pons and medulla. Spastic dysarthria has a harsh, strained, mechanical quality. Words are spoken slowly and with great effort. On examination, the jaw jerk and gag reflex may be brisk. Important causes of spastic dysarthria are amyotrophic and primary lateral sclerosis (Chap. 10), progressive supranuclear palsy (Chap. 13), Wilson disease (Chap. 14), and the pseudobulbar state (see below).

Flaccid (Lower Motor Neuron) Dysarthria

Patients with flaccid dysarthria have thick, muddy speech, usually secondary to generalized disorders of the motor neuron, neuromuscular junction, or muscle. Common causes include amyotrophic lateral sclerosis, bulbar myasthenia gravis, and oculopharyngeal muscular dystrophy. Individual neuropathies of the facial, hypoglossal, and vagus nerves may also cause flaccid dysarthria. The standard technique to differentiate among these mononeuropathies is to test labial, lingual, and guttural sounds. In clinical practice, however, these tests play a somewhat limited role, as cranial mononeuropathies are uncommon and, even if present, are usually suggested by neighborhood signs rather than the pattern of dysarthria. Nonetheless:

- The facial nerve innervates the lips and other muscles of facial expression. Facial nerve lesions cause difficulties to produce labial sounds such as “puh.”
- The hypoglossal nerve innervates the tongue. Hypoglossal nerve lesions lead to difficulties producing lingual sounds such as “tuh.”
- The vagus nerve innervates the laryngeal muscles. Lesions of this nerve produce difficulties with making guttural sounds such as “kuh” or “guh.” Injury to the vagus nerve, and more specifically its recurrent laryngeal branch, however, is more likely to produce hoarseness or raspiness.

Extrapyramidal Dysarthrias

Tremor, myoclonus, chorea, and tics are manifestations of extrapyramidal disease that may affect speech in ways analogous to the ways that they affect the limbs. Moderate-to-severe Parkinson disease is usually accompanied by hypophonic (reduced in volume) and monotonous speech. Spasmodic dysphonia is a dystonic disorder of the laryngeal muscles: in adductor spasmodic dysphonia, speech is cut off and choppy, while in abductor spasmodic dysphonia, speech is breathy and whispery. Spasmodic dysphonia, similar to the other focal dystonias, may be treated with botulinum toxin injections. Multisystem atrophy may produce a characteristic high-pitched, quivering dysarthria.

Scanning Dysarthria

This is the classic speech pattern in patients with disease of the cerebellum and its connections. The speech has a halting, uncoordinated pattern with awkward volume modulations and separations between words and phrases. Accents are put on the wrong syllables. The best-known cause of scanning speech is advanced multiple sclerosis, but ischemic, inflammatory, and neoplastic disorders of the cerebellum and its connecting pathways may also produce it.

"Slurred" Speech

Unfortunately, many patients with acute dysarthria do not fit neatly into one of the four most common subtypes described in this section and are labeled with nonspecific "slurred speech." This is common in patients with substance intoxications or metabolic disturbances. Stroke, particularly in the subcortical white matter, may produce isolated slurring of speech, but the slurred speech is usually accompanied by facial or hand weakness or by a language disturbance.

Dysphagia

Swallowing is divided into oral, pharyngeal, and esophageal phases. The first important task in evaluating dysphagia, therefore, is to determine which swallowing phase is dysfunctional by asking the patient where the food gets stuck. If they point to the mouth (oral phase) or back of the throat (pharyngeal phase), the dysphagia may be due to neurologic dysfunction. If they point instead to the sternum, they have an esophageal problem and should be referred to a gastroenterologist. It is also important to determine which consistencies are difficult for the patient to swallow. Dysphagia for liquids or nasal regurgitation during swallowing strongly suggests neurologic disease. In some cases, it may be difficult to determine whether dysphagia is caused by oral or pharyngeal phase dysfunction and video swallowing studies may help to localize the site of pathology. Many of the causes of dysphagia discussed below are irreversible, and patients must be treated with dietary restrictions or, when dysphagia is severe, feeding tubes to reduce the risk of aspiration.

Oral Phase Dysphagia

Trigeminal Nerve Lesions

The muscles of mastication are innervated by the trigeminal nerve. Because trigeminal nerve lesions rarely produce dysphagia, they will not be discussed further.

Hypoglossal Nucleus and Nerve Lesions

Supranuclear control of tongue movement is derived from the lower third of the precentral gyrus. The lower motor neurons are in the dorsomedial medulla (Chap. 21,

Fig. 21.2). These motor neurons give rise to the hypoglossal nerve fascicles which course anteriorly through the medulla, passing through the corticospinal tracts to emerge from the medulla. After traversing the hypoglossal canal, the nerve takes a long course through the neck, looping around the internal carotid artery, external carotid artery, and internal jugular vein before supplying the muscles of the tongue. Most tongue muscles have bilateral cortical innervation, while the genioglossus has predominantly contralateral innervation.

When examining a patient with suspected tongue weakness or oral phase dysphagia, first observe the tongue as it rests in the floor of the mouth. Look for atrophy, particularly scalloping at the edges. Also look for fasciculations or wriggling movements of the tongue. Both atrophy and fasciculations suggest motor neuron disease. Next, ask the patient to stick their tongue out straight. Deviation to one side suggests either an ipsilateral hypoglossal nuclear or nerve lesion or a contralateral hemispheric lesion. Finally, ask the patient to place their tongue into their cheek. Look for asymmetries in resistance as you press the tongue inwards through the outside of the cheek.

The first common localization of tongue weakness is the motor neurons of the hypoglossal nucleus, as occurs in amyotrophic lateral sclerosis. Tongue weakness in motor neuron disease is almost always accompanied by other signs, as discussed in Chap. 10. Infarction of the hypoglossal nerve fascicles within the medial medulla is the next common cause of tongue weakness. Because the fascicles cross through the corticospinal tract, patients with fascicular lesions will have contralateral hemiparesis (the medial medullary syndrome of Dejerine). Hypoglossal nerve lesions within the posterior fossa are often due to trauma or to mass lesions and affect the glossopharyngeal, vagus, and accessory nerves simultaneously. Finally, lesions of the hypoglossal nerve within the neck may be the result of carotid dissection, carotid endarterectomy, or retropharyngeal masses.

Pharyngeal Phase Dysphagia

Supranuclear Lesions (the Pseudobulbar State)

Because the motor neurons of the nucleus ambiguus (see below) receive supranuclear inputs from both hemispheres, unilateral lesions do not produce dysphagia. Bilateral lesions, however, occur in patients with the "pseudobulbar state" characterized by dysphagia, spastic dysarthria, and emotional incontinence. Muscles of the lower part of the face and tongue are weak, and the gag reflex is usually hyperactive. A patient with emotional incontinence laughs or cries excessively in situations that are only mildly funny or sad. In some cases, they may burst out laughing or cry unexpectedly in response to mundane news. Attacks are frequent and spontaneous. Though the patient is not emotionally bothered by these symptoms, attacks may be socially embarrassing. The main causes of the pseudobulbar state are subcortical white matter ischemia, demyelination, and motor neuron disease. Unfortunately,

treatments for dysphagia related to supranuclear lesions are limited. Pathologic laughter and crying, however, may improve with antidepressants or the combination of dextromethorphan and quinidine [7].

Nuclear Lesions

The nucleus ambiguus within the lateral medulla contains the motor neurons that mediate swallowing. The classic lesion of the lateral medulla is the Wallenberg syndrome due to vertebral or posterior inferior cerebellar artery infarction (Chap. 21). Adjacent brainstem structures including the vestibular nuclei, the Horner tract, the spinal trigeminal tract and nucleus, and the spinothalamic tract will be involved in the Wallenberg syndrome. Other causes of nuclear lesions include amyotrophic lateral sclerosis, tumors, demyelinating disease, and syringobulbia.

Glossopharyngeal and Vagus Nerve Lesions

The glossopharyngeal and vagus nerves contain motor, sensory, and parasympathetic fibers. They are often discussed together because they arise from shared brainstem structures, lie in proximity to each other as they exit the brainstem, and perform similar functions. The motor neurons of the nucleus ambiguus give rise to the components of the glossopharyngeal and vagus nerves that govern swallowing. The nerves may be affected in isolation or in combination:

- Because stylopharyngeus is the only pharyngeal muscle innervated by the glossopharyngeal nerve, isolated nerve lesions produce only mild dysphagia. Clinical signs of glossopharyngeal nerve lesions include loss of taste on the posterior 1/3 of the tongue and a decreased gag reflex.
- The vagus nerve innervates all the pharyngeal muscles with the exception of stylopharyngeus, so isolated vagus nerve lesions lead to severe dysphagia. Because the vagus nerve also innervates the laryngeal muscles, a lesion of this nerve will also produce hoarseness. Clinical signs of vagus nerve lesions include decreased ipsilateral palate elevation and a decreased gag reflex.
- After emerging from the lateral medulla, the glossopharyngeal and vagus nerves exit the skull with the accessory nerve through the jugular foramen. In addition to the signs and symptoms of glossopharyngeal and vagus nerve lesions, jugular foramen pathology produces accessory nerve dysfunction including weakness of the ipsilateral sternocleidomastoid (preventing head turning in the *contralateral* direction) and ipsilateral trapezius (preventing ipsilateral shoulder shrug).

Neuromuscular Junction Lesions

Bulbar myasthenia gravis is an important, treatable cause of dysphagia that often leads to urgent hospitalization (Chap. 10). Agents such as pyridostigmine are ineffective for bulbar myasthenia, as the patient cannot swallow their medications. Intravenous pyridostigmine (1–2 mg) may be used as a temporizing measure, but almost all patients with severe bulbar myasthenia gravis should be treated with

intravenous immunoglobulin or plasmapheresis as if they were in myasthenic crisis (Chap. 12). Botulism is the other important neuromuscular junction disorder that causes pharyngeal dysphagia (Chap. 12).

Myopathic Lesions

Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant disorder characterized by bilateral ptosis (usually the first and more prominent symptom) and dysphagia [8]. Extraocular muscle weakness may occur but is usually not a prominent feature. Unlike most muscular dystrophies, symptoms typically develop in middle age, and it may take years before they are identified. The diagnosis is straightforward when there is a positive family history. If this is not available, sequencing of the PABPN1 gene helps to establish the diagnosis. Although cricopharyngeal myotomy may help dysphagia in some patients with OPMD, treatment is largely supportive.

Inflammatory myopathies and mitochondrial myopathies may on occasion present with dysphagia as the first symptom.

Extrapyramidal Lesions

Bradykinesia of swallowing is often a later feature of extrapyramidal disorders such as Parkinson disease. It is not present at disease onset or initial diagnosis.

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Dizziness and Vertigo

9

"What Do You Mean by Dizziness?"

The first step in evaluating the patient with dizziness is to determine precisely what they mean when they tell you that they are dizzy. Unfortunately, descriptions provided by patients are notoriously vague and often differ when the history is repeated [1]. Nevertheless, an accurate clinical history with description of the symptoms is required to make a diagnosis. The three sensations which patients describe most commonly when they use the term "dizziness" are lightheadedness, imbalance, and vertigo. While all three are of potential interest to the neurologist, it is vertigo that is most specific for neurologic disease. Lightheadedness and imbalance will therefore be discussed only briefly.

Lightheadedness

Although lightheadedness or presyncope is usually the province of internists and cardiologists, many patients with frequent, intolerable symptoms are referred to neurologists for evaluation and treatment. After performing a careful history, it is necessary to review the cardiac data, including electrocardiograms, echocardiograms, and telemetry, to make sure that there is no cardiac explanation for the symptoms. Ensure that the patient is not volume depleted, and check for any recent changes in antihypertensive medications or sedatives. For patients in whom the cause of lightheadedness is still in question, tilt-table testing and extended cardiac telemetry (i.e., a Holter or implantable monitor) may help to distinguish among cardiogenic syncope, orthostatic hypotension, neurally mediated syncope, and postural orthostatic tachycardia syndrome.

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Cardiogenic Syncope

Arrhythmias, aortic stenosis, and hypertrophic obstructive cardiomyopathy are common and serious cardiogenic causes of presyncope and syncope that require the attention of a cardiologist.

Orthostatic Hypotension

Orthostatic hypotension is defined as a drop in systolic blood pressure of more than 20 mm Hg or diastolic blood pressure of more than 10 mm Hg which occurs within 3 minutes of standing [2]. Orthostatic hypotension is often secondary to antihypertensive medications or volume depletion. Primary neurologic conditions that predispose to orthostatic hypotension include autoimmune autonomic neuropathies (specifically those associated with antibodies to ganglionic acetylcholine receptors), multisystem atrophy, pure autonomic failure, and Parkinson disease. Conservative measures to treat orthostatic hypotension include adjusting any contributing medications, encouraging adequate hydration, increasing salt intake, and raising the head of the bed at night. Elastic stockings and abdominal binders to reduce peripheral venous pooling are other non-pharmacologic options but are poorly tolerated by many patients, especially in the summer. If conservative measures fail, the two main medical options are the mineralocorticoid fludrocortisone (initiated at 0.1 mg qd and titrated to 0.5 mg qd as needed) and the α-adrenergic agonist midodrine (initiated at 2.5 mg tid and increased to 10 mg tid as tolerated). Do not give either agent in the evening, as doing so may produce nocturnal hypertension and worsen daytime hypotension. Both agents may produce supine hypertension as a side effect. Pyridostigmine at a dose of 60 mg tid may offer modest benefit to patients with orthostatic hypotension [3]. Exercise in the recumbent position may be effective for some patients with orthostatic hypotension.

Neurally Mediated Syncope

Neurally mediated syncope (the vasovagal response) is a complex and incompletely understood phenomenon. It occurs as a result of peripheral vasodilatation and bradycardia secondary to increased vagal output to the sinus node of the heart. Neurally mediated syncope is most often provoked by a painful, stressful, or emotional stimulus. Other common precipitants include urination, defecation, and the Valsalva maneuver. Carotid sinus syncope is a rare form of neurally mediated syncope which results from pressure in the area of the carotid artery or sudden head turning. Lightheadedness in neurally mediated syncope is accompanied by weakness, tremulousness, blurred vision, diaphoresis, and nausea. If the diagnosis is not obvious from the history, it may be made with the help of tilt-table testing. Patients with neurally mediated syncope should be educated on how to identify and avoid precipitants of their attacks. Volume expansion and fludrocortisone may be helpful.

Postural Orthostatic Tachycardia Syndrome (POTS)

POTS is a poorly understood disorder in which lightheadedness or fainting occurs upon standing and is associated with tachycardia but not with a fall in blood pressure. Accompanying symptoms resemble those of neurally mediated syncope, but patients frequently have multiple symptoms outside of simple orthostasis, similar to patients with the diagnosis of fibromyalgia. Most patients with POTS are young women, and because the symptoms which accompany POTS may resemble panic attacks, patients are often misdiagnosed with anxiety disorders before the correct diagnosis is contemplated. POTS is diagnosed by finding a symptomatic increase in heart rate of more than 30 beats per minute without a drop in blood pressure upon standing [4]. Unfortunately, treatments such as volume repletion, fludrocortisone, and midodrine usually do not produce a meaningful improvement.

Imbalance

Imbalance is a sensation that is often difficult to describe more specifically than "dizziness." Some patients will use the term "off balance" or may tell you that they feel as if they are on a ship at sea. Imbalance has many causes, but in general, they all have some component of proprioceptive loss secondary to cervical myelopathy, polyneuropathy, and orthopedic conditions. Evaluation and treatment of imbalance are discussed further in Chap. 18.

Evaluation of Vertigo

History

Vertigo is the sensation of environmental movement or rotation produced by dysfunction of the vestibular labyrinth, vestibular nerve, brainstem, or cerebellum. As a general rule, peripheral (labyrinthine and vestibular nerve) dysfunction is benign, while central (brainstem and cerebellar) dysfunction is serious and possibly life-threatening. Distinction between central and peripheral localizations is therefore crucial to determine which patients require immediate evaluation. *The most reliable indicator of central vertigo is the presence of accompanying features of central nervous system dysfunction such as diplopia, facial numbness, dysarthria, and dysphagia.* Features that are more consistent with (but not pathognomonic for) peripheral nervous system pathology include hearing loss, aural fullness, and tinnitus. Several other features may also help to distinguish between central and peripheral nervous system dysfunction but are not reliable. For example, symptom duration of several minutes is more likely to reflect a central process, whereas symptoms which last for seconds at a time are more consistent with peripheral disease. Occipital or nuchal headaches are more typical of central nervous system processes such as cerebellar or brainstem hemorrhages. Changes in symptoms with head position are

more characteristic of peripheral nervous system disorders. Older patients and those with risk factors for vascular disease are more likely to have central vestibular dysfunction than are younger, otherwise healthy people.

Neurologic Examination

Neurologic examination is often more helpful than the history in distinguishing between central and peripheral causes of vertigo. Cranial nerve findings including anisocoria, ocular misalignment, facial numbness, facial weakness, asymmetric hypoactive gag reflex, and tongue deviation favor brainstem pathology (Chaps. 7 and 8). Any weakness or sensory deficits in the limbs also points to a brainstem process. Hearing loss more commonly accompanies peripheral causes of vertigo. The following examination techniques are helpful in assessing the vertiginous patient.

"Cerebellar" Signs

For clinical purposes, the cerebellum may be divided into the midline which coordinates truncal movements and the hemispheres which coordinate appendicular movements. The following examination techniques help to assess pathology in the cerebellum or its connections within the brainstem and cerebral hemispheres:

Finger-to-Nose Test

Limb dysmetria may be elicited by asking the patient to move their finger rapidly back and forth between their nose and your finger. In order to maximize the yield of this task, instruct the patient to abduct their arm so that the elbow is at shoulder height and place the target an entire arm's length away from them. A patient with ipsilateral cerebellar hemispheric dysfunction will miss or overshoot the target and may also miss their nose or strike it with excessive force. In some patients with cerebellar system dysfunction, finger-to-nose testing will uncover intention tremor, a tremor that worsens or manifests near the end of a directed movement (Chap. 14).

Overshoot

The overshoot phenomenon is elicited by having the patient attempt to perform mirror movements. Instruct them to align their hand opposite yours and then mirror your hand as you move it rapidly in the vertical or horizontal planes and then stop it abruptly. A patient with an ipsilateral cerebellar hemispheric lesion will not be able to stop in time, terminating their movements several inches past the target and then making a corrective movement to reach the target.

Rebound

Ask the patient to extend their arms in front of them with their hands pronated. Tap the dorsal surfaces of each forearm briskly, observing for abnormal, large-amplitude oscillations as the arm returns to its resting position. Rebound points to an ipsilateral cerebellar hemispheric lesion.

Heel-Knee Shin Test

Instruct the patient to tap the distal shin with the opposite heel and then run it up and down the surface of the shin. Clumsiness or an inability to complete this kind of movement points to an ipsilateral cerebellar hemispheric lesion.

Truncal Ataxia

Patients with midline cerebellar lesions are unable to sit upright, tending to fall to the side with any perturbation of the trunk. Patients with hemispheric lesions tend to fall to the side of the lesion.

Nystagmus

Nystagmus is an ocular oscillation initiated by an abnormal slow movement and followed by a fast corrective movement in the opposite direction. By convention, it is named for the direction of the fast phase. Examine for nystagmus in primary position (with the eyes looking straight ahead) and in all directions of gaze, noting the direction, amplitude, and velocity of nystagmus in each position. Subtle nystagmus may be observed only when visual fixation is removed. The best way to do this at the bedside is to have the patient close one eye while you visualize the other eye with an ophthalmoscope. When examining for nystagmus using this method, keep in mind that the fundus moves in the direction opposite to the direction that the eye moves when it is opened. A detailed discussion of the neuroanatomy of nystagmus is beyond the scope of this text. For clinical purposes, the following are several rules of thumb for interpreting nystagmus [5]:

- Endpoint nystagmus is a low-amplitude, low-frequency nystagmus that occurs with ocular fixation. It fatigues after two to three beats and is usually a normal variant.
- Horizontal and horizontal-torsional nystagmus suggests contralateral peripheral vestibular dysfunction, often vestibular neuritis. This nystagmus may be present in primary position but is usually more prominent when looking in the direction of its fast phase.
- Horizontal nystagmus which reverses direction every 2 minutes is called periodic alternating nystagmus and points to dysfunction of the cerebellar midline.
- Horizontal nystagmus which is relatively symmetric in all directions of gaze is usually congenital. People with this form of nystagmus do not have disabling oscillopsia (the sensation that objects are moving back and forth). It is important to recognize this form of nystagmus, as it may lead to unnecessary evaluation if it is misinterpreted.
- Bruns nystagmus suggests a cerebellopontine angle mass: when gaze is directed towards the side of the mass, there is a large-amplitude horizontal nystagmus due to brainstem compression, and when the gaze is directed to the contralateral side or in primary position, there is a small-amplitude horizontal nystagmus away from the tumor due to vestibular paralysis [6].
- Downbeating nystagmus in primary position or with lateral gaze suggests vestibulocerebellar dysfunction, medication toxicity, or cervicomedullary junction lesion such as a Chiari malformation [7].

- Purely upbeating nystagmus points to drug intoxication or to medullary dysfunction. Unless there is a clear history of intoxication with a medication or drug abuse, pure vertical nystagmus should prompt evaluation for brainstem and cerebellum pathology.
- Upbeating, torsional nystagmus elicited by the Dix-Hallpike maneuver, is classical for benign paroxysmal positional vertigo.
- Purely torsional nystagmus is uncommon and points to brainstem rather than peripheral vestibular dysfunction.
- Almost all nystagmus involves both eyes. Causes of true or apparent monocular nystagmus include:
  - Myasthenia gravis
  - Internuclear ophthalmoplegia, involving the abducting eye (Chap. 6)
  - Congenital monocular blindness
  - Superior oblique myokymia

Several abnormal eye movements may be misinterpreted as nystagmus:

- Ocular bobbing and dipping are seen in comatose patients with brainstem dysfunction and are discussed further in Chap. 2.
- Square-wave jerks are binocular saccadic movements that occur in the direction opposite to visual fixation and last for a fraction of a second before the eyes return to primary position. They are frequent in normal subjects but may also occur in patients with Parkinsonian syndromes, especially progressive supranuclear palsy and multisystem atrophy [8].
- Opsoclonus is characterized by irregular, sometimes chaotic, horizontal and vertical eye movements. It is often present in conjunction with myoclonus (Chap. 14) and is secondary to a paraneoplastic syndrome or to autoimmune disease.

Head-Thrust Test

A positive head-thrust test is useful in establishing the presence of a unilateral peripheral vestibular lesion [9]. To perform the test, instruct the patient to fix their gaze on a target approximately 10 feet away. Next, grasp the head by the vertex and chin, and quickly rotate it horizontally by about 20°. In a patient with a unilateral vestibular lesion, rotation of the head *towards* the affected side will require a corrective saccade opposite to the direction of head rotation to keep the eyes on the target because the vestibulo-ocular reflex is impaired. Rotation of the head *away* from the affected side will be accompanied by normal eye movements without any refixation.

Dix-Hallpike Maneuver

The Dix-Hallpike maneuver is essential to the diagnosis of benign paroxysmal positional vertigo (BPPV) [10]. To perform the Dix-Hallpike maneuver, the patient should be seated upright (Fig. 9.1a). Warn the patient that the maneuver may lead to intense vertigo. Grasp the head on both sides, and quickly turn it to the side while bringing the patient backwards so that the head lies over the edge of the bed (Fig. 9.1b). When the Dix-Hallpike maneuver is performed on patients with the

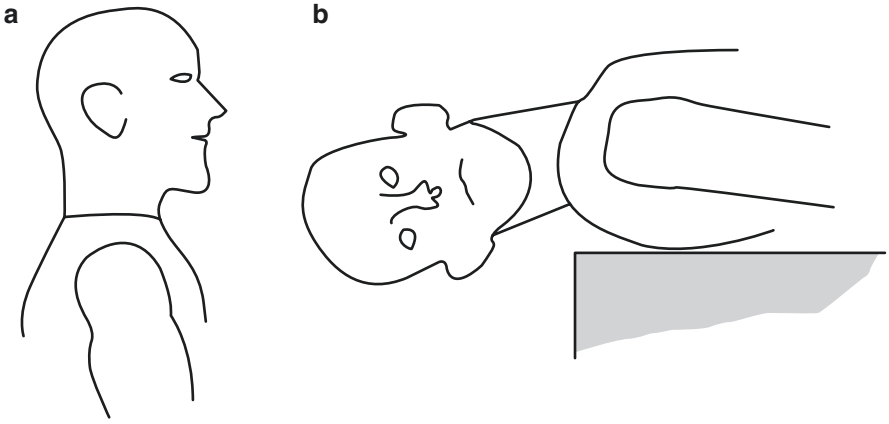

Fig. 9.1 The Dix-Hallpike maneuver for right-sided BPPV. See text for details

posterior canal variant of BPPV (see below), it produces a torsional upbeat nystagmus beating towards the side of the involved ear. Characteristically, this maneuver fatigues when it is repeated. It is important to keep the head turned and hanging over the side of the bed after performing the maneuver, as nystagmus secondary to BPPV is usually associated with a latency of up to 30–45 seconds. A less common variant of BPPV involves the horizontal semicircular canal, in which case the nystagmus beats horizontally towards the involved ear. The Dix-Hallpike maneuver should be performed both to the left and to the right.

Imaging of the Patient with Vertigo

The need for neuroimaging in patients with signs and symptoms of a central source of vertigo is clear-cut. The studies of choice are MRI of the brain with MRA of the posterior circulation. CT scans do not provide adequate images of the posterior fossa and are therefore of limited value in evaluating patients with suspected central vertigo unless it is due to cerebellar hemorrhage or a mass with new edema. Patients with brief episodes of vertigo and an examination that is normal or shows only horizontal nystagmus generally do not require neuroimaging. Such patients usually have peripheral vestibulopathies, though a rare patient with a limited posterior inferior cerebellar artery infarction may present in the same way [11]. It is prudent to image older patients and those who have risk factors for vascular disease if any uncertainty remains about the localization after the history and physical examination.

Causes of Vertigo

Vertebrobasilar Ischemia and Infarction

Vertebrobasilar disease is the most dangerous cause of acute-onset vertigo. Symptoms begin suddenly, and some patients have transient ischemic attacks before

stroke occurs. Because the typical involvement of blood vessels of the posterior circulation is in a patchy, irregular manner, there is considerable variability in the presentation of vertebrobasilar strokes. Consider vertebral artery dissection in patients with posterior circulation strokes accompanied by neck pain (Chap. 21). Signs and symptoms which accompany vertigo are highly variable and include diplopia, facial pain and numbness, dysarthria, dysphagia, and sensorimotor dysfunction in the limbs. The diagnosis of vertebrobasilar infarction is confirmed by MRI. MRA or CTA of the head and neck are frequently helpful in identifying the responsible vessel.

Vestibular Neuritis

Presumed viral infection of the vestibular nerve is among the most common causes of acute vertigo. A viral prodrome may or may not precede vestibular neuritis. Symptoms usually develop over several hours to days and last for up to a few weeks at a time. Vertigo is typically quite severe and is associated with nausea and vomiting. Some patients have a combination of vestibular neuritis and hearing loss known as neurolabyrinthitis. The nystagmus due to vestibular neuritis is either horizontal or horizontal with a torsional component and directed away from the involved ear. A positive head thrust test helps to establish the diagnosis. There is no specific treatment for the underlying cause of vestibular neuritis. Supportive care includes vestibular suppressants such as the antihistamine meclizine (25–50 mg q6h) or the benzodiazepine lorazepam (0.5–1 mg q6h), though these medications may delay habituation. Patients with severe or persistent symptoms may require vestibular rehabilitation.

Benign Paroxysmal Positional Vertigo (BPPV)

BPPV is characterized by brief (less than 30–60 seconds), episodic vertigo which occurs with changes in head position, often when turning over in bed or bending the head backwards while reaching for something on a high shelf. Because of the intensity of the episodes, patients may report that symptoms last for up to a few minutes a time. Precipitating factors include head trauma, vestibular neuritis, and perilymph fistula. The vertigo and nystagmus of BPPV are caused by excessive stimulation of the cupula by otoconial debris in the semicircular canal which in turn leads to increased firing of the ampullary nerve. The diagnosis is established via the Dix-Hallpike maneuver (see above). In patients with the posterior semicircular canal variant of BPPV, this maneuver produces nystagmus which is upbeating and torsional towards the lower ear. In patients with the less common horizontal canal variant, the nystagmus is horizontal and beats towards the lower ear. Nystagmus may occur in the opposite direction in patients recovering from acute BPPV or be absent entirely.

The Epley particle-repositioning maneuvers are an effective treatment for patients with the posterior semicircular canal variant of BPPV (Fig. 9.2) [12]:

1. The patient should be seated upright (Fig. 9.2a).
2. Instruct them to turn the head 45° towards the symptomatic side (Fig. 9.2b).

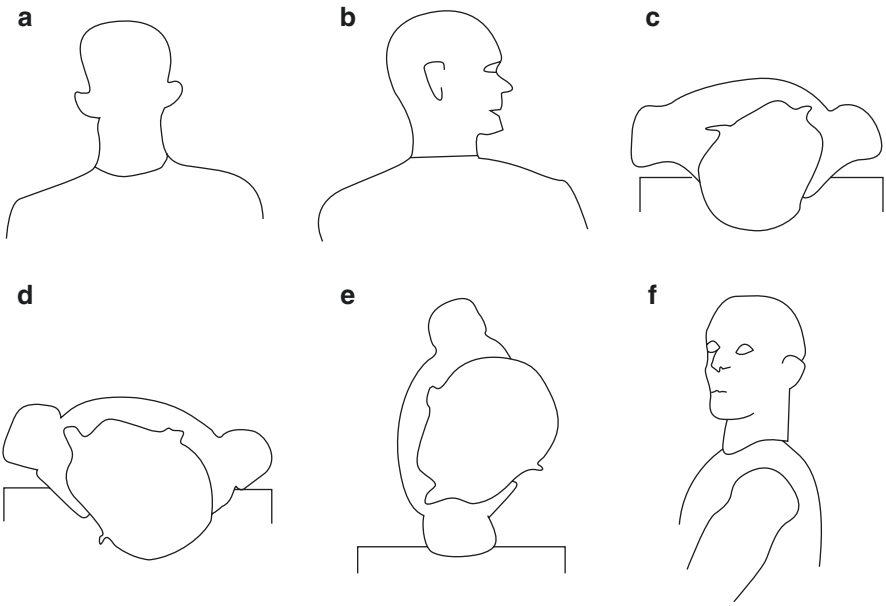

Fig. 9.2 The Epley maneuvers for right posterior canal variant BPPV. See text for details

3. Next, they should bring their head backwards so that they are lying over the edge of the bed (Fig. 9.2c). They should wait 30 seconds in this position.
4. Next, they should rotate their head 90° so that they are facing in the opposite direction (Fig. 9.2d). Wait 30 seconds in this position.
5. Next, instruct the patient to rotate the entire head and body 90° (onto the unaffected shoulder), and wait for 30 seconds in this position (Fig. 9.2e).
6. Finally, instruct the patient to sit up while keeping the head rotated 45° with respect to the body. Wait 30 seconds in this position (Fig. 9.2f).

In some patients with BPPV, the vertigo may be so severe that the Epley maneuvers are poorly tolerated. These patients may benefit from pre-treatment with vestibular suppressants such as meclizine. Symptoms may recur, and providing written instructions or pictures on how to perform the Epley maneuvers at home is helpful. In patients with symptoms that do not respond after the first attempt at the Dix-Hallpike maneuver, remaining upright for 24 hours after the maneuvers are performed may be helpful.

Treat the horizontal variant of BPPV with the barbecue spit maneuver (Fig. 9.3) [13]. The patient lies supine (Fig. 9.3a) and then rotates 90° so that the affected ear is facing downwards (Fig. 9.3b). Instruct them to wait for 30 seconds in this position. The patient then completes three successive 90° rotations, waiting for 30 seconds in between each rotation (Fig. 9.3c–e). The forced prolonged position method is another option for the horizontal canal variant of BPPV in which the patient lies supine with the head turned to the unaffected side for 6–12 hours [14].

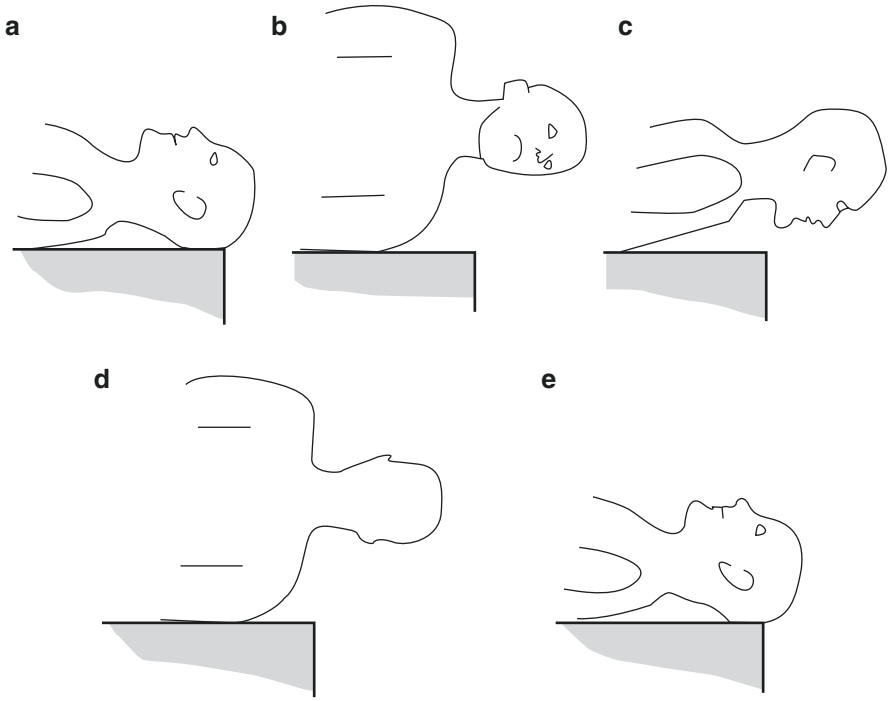

Fig. 9.3 The barbecue spit maneuvers for right horizontal canal variant BPPV. See text for details

Meniere Disease

Meniere disease is thought to be the result of endolymphatic fluid buildup in the inner ear with disturbance of the normal potassium concentration in the environment of the vestibular nerve. The classical symptom cluster of Meniere disease is recurrent, spontaneous vertigo, sensorineural hearing loss, aural fullness, and tinnitus [15]. The diagnosis may be overlooked in its early stages when vertigo is the sole symptom. Episodes of vertigo last for between 20 minutes and a few hours. Several days of milder imbalance may follow the intense vertiginous spells. During attacks, low-frequency hearing loss may be detected with a 256 Hz tuning fork, although formal audiometric testing is usually required. Hearing loss progresses with recurrent attacks. Prophylaxis for Meniere disease includes salt restriction and diuretics such as hydrochlorothiazide (50 mg qd) or acetazolamide (500 mg bid). Acute attacks respond to vestibular suppressants. Patients with refractory symptoms should be referred to an otorhinolaryngologist for consideration of endolymphatic sac surgery, transtympanic gentamicin, or labyrinthectomy [16].

Migraine

When vertigo occurs as a migraine aura (Chap. 19), the diagnosis is straightforward. More difficult from a diagnostic perspective, however, are attacks of vertigo in migraineurs which last for hours to days and occur independently of the headaches. This scenario is often seen in perimenopausal women [17]. Patients with such

episodes are often diagnosed with Meniere disease or chronic undifferentiated dizziness. Overall, migraine-associated dizziness accounts for only 2% of episodic dizziness, and other more common conditions should be excluded prior to committing to this diagnosis [18]. Migraine abortive and prophylactic agents may help reduce attack frequency.

Medication Toxicity

Vestibulotoxic medications that commonly produce vertigo include aminoglycosides, anticonvulsants, sedatives, and cisplatin. In some but not all cases, discontinuing the responsible medication may reverse the symptoms.

Perilymph Fistula

This condition results from a leakage of perilymph fluid through the labyrinthine membrane. The classic constellation of symptoms is a popping sound in the ear accompanied by a sudden hearing loss, tinnitus, and vertigo. Symptoms are precipitated by sneezing, straining, and coughing. The diagnosis is established by finding a positive fistula sign: symptoms are reproduced when the patient attempts to "pop" their ears while squeezing their nose closed. Instruct patients with perilymph fistula to avoid precipitating activities and to take vestibular suppressants such as meclizine during acute attacks. Refer patients with refractory symptoms to an otorhinolaryngologist for definitive treatment.

Epileptic Dizziness

In rare circumstances, a sudden brief feeling of instability or frank vertigo may be a seizure manifestation, classically localizing to the parietal lobe but in practice more commonly arising from the temporal lobe [19, 20]. Isolated vertigo is rare, and most patients have other seizure manifestations. Ictal bradycardia (and even asystole) may also be a seizure manifestation, arising more commonly from the left than the right temporal lobe [21]. Epileptic dizziness or vertigo should be considered only after more common conditions are thoroughly excluded. Because it so uncommon, epileptic dizziness must be confirmed with an EEG demonstrating epileptiform discharges during an episode.

Cerebellopontine Angle (CPA) Tumors

Acoustic neuromas and meningiomas are the most common tumors of the cerebellopontine angle (Chap. 23). These tumors generally grow slowly, and compensation from the contralateral vestibular system makes acute vertigo uncommon [22]. Other symptoms of CPA tumors include facial numbness, facial weakness, hearing loss, and disequilibrium. Surgical intervention should be considered for patients with progressive symptoms or evidence of tumor expansion on serial neuroimaging studies [22].

Cervicogenic Dizziness and Vertigo

Patients with cervical spondylosis or other disorders of the upper cervical spine may experience nonspecific dizziness or frank vertigo, presumably due to compression of proprioceptive fibers within the spinal cord. The entity is controversial and is

considered a diagnosis of exclusion. Treatment with a soft cervical collar or cervical decompressive surgery in patients with other signs of cervical myelopathy may prove effective, though high-quality data to support any intervention are lacking.

Chronic Undifferentiated Dizziness

This diagnosis may represent a forme fruste of migraine, Meniere disease, or vestibular neuritis. Many patients with this condition are dismissed as having psychiatric disorders. A viral prodrome or mild head trauma frequently precedes symptom onset by several weeks, but it is hard to prove that either process is responsible. Most patients describe a sense of being off balance rather than frank vertigo. They do not usually have hearing problems, ocular motility disorders, or falls. Examination is normal with the possible exception of subtle horizontal nystagmus. Chronic undifferentiated dizziness is a diagnosis of exclusion. A thorough evaluation should include electronystagmography, caloric testing, and focused neuroimaging studies. Some patients respond to vestibular rehabilitation and vestibular suppressant medications. Agents used for migraine prophylaxis may help a small minority.

Postconcussion Syndrome and Posttraumatic Dizziness

The postconcussion syndrome includes headache, irritability, forgetfulness, poor concentration, and dizziness (Chap. 4). The dizziness is often due to labyrinthine trauma or BPPV. In many cases, however, the dizziness of postconcussion syndrome is a vague sense of imbalance rather than true vertigo.

Multiple Sclerosis

Demyelinating lesions involving the cerebellum or its connections within the brainstem may lead to vertigo (Chap. 22). Dizziness or vertigo is not the presenting or sole feature of MS in most cases, however.

Paraneoplastic Cerebellar Degeneration

The most common antibodies which lead to paraneoplastic cerebellar degeneration are anti-Yo (breast and ovarian cancers), anti-Hu (small-cell lung cancer), anti-Tr (Hodgkin lymphoma), and anti-Ri (breast and ovarian cancers) [23]. Treatment should focus on the underlying cancer. Unfortunately, the ataxia associated with these syndromes is progressive, and most patients lose the ability to ambulate.

Episodic Ataxia

The episodic ataxias are a group of uncommon channelopathies characterized by recurrent bouts of ataxia [24]. Episodic ataxia type 2, in particular, may cause episodic vertigo and headaches which are precipitated by stress and fatigue and which may last for hours or days at a time. Acetazolamide (500–1000 mg) reverses the symptoms of an acute attack and may prevent recurrence.

Dizziness of Psychological Origin

Patients with anxiety and panic disorders may describe a sensation of dizziness that has features distinct from vertigo, including a sensation of floating, lightheadedness, or depersonalization. These patients often come to neurological attention when other symptoms of a panic attack are absent. Careful psychiatric assessment and exclusion of syncope and neurologic disorders help to make the diagnosis. Pharmacological and behavioral management of the responsible anxiety or panic disorder may reduce or cure symptoms.

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Proximal and Generalized Weakness

10

Weakness and Its Mimics

Weakness is defined as the failure of a movement to generate an appropriate force and is both a sign and a symptom of motor dysfunction. Careful questioning of many patients referred for weakness reveals that the problem is not actually weakness, but rather a condition which mimics it:

- Fatigue is the common sensation of tiredness or physical exhaustion that accompanies conditions such as hypothyroidism, anemia, sleep disorders, and depression. Although fatigued patients often describe themselves as weak, formal motor testing shows that they actually possess full strength.
- Bradykinesia is slowness of movement. It is a core feature of parkinsonism and is discussed in greater detail in Chap. 13.
- Musculoskeletal system dysfunction may reduce the range of motion of a joint, but it does not produce actual weakness.
- Pain from any source may restrict movement and be erroneously interpreted as weakness.
- Sensory loss that impairs joint position sensation may lead to the impression of weakness. The telltale sign that sensory loss is the cause of impaired movement is that a patient can move a joint normally when looking at it, but not when looking away.

The Evaluation of Weakness

History

The first step in diagnosing the weak patient is to define the distribution and speed of onset of weakness by history and physical examination. The most common gradual onset patterns of weakness are:

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- Proximal (this chapter)
- Distal (Chap. 15)
- Extraocular muscle (Chap. 6)
- Focal limb (Chap. 11)
- Bulbar (Chap. 8)
- Facial (Chap. 8)
- Myelopathic (Chap. 17)

Rapidly developing weakness is discussed further in Chaps. 12 and 21.

Even if the history strongly suggests one of these patterns, it is imperative to perform a comprehensive neurologic exam. Patients are frequently unaware of or adapt to minor weakness, and you will miss subtle signs of more widespread motor system dysfunction if you attend to only the weakness that the patient describes. This is often true for patients with amyotrophic lateral sclerosis, in whom the diagnosis is routinely overlooked for several months due to exclusive focus on a single weak muscle group.

Muscle Bulk

While it is tempting to proceed directly to power testing when evaluating a weak patient, examination of muscle bulk offers important diagnostic clues. Look for muscle atrophy in both proximal and distal muscles, around the temples, and in the tongue. Muscles in which atrophy is readily detectable include the deltoid, periscapular muscles, abductor pollicis brevis, first dorsal interosseous, quadriceps, and extensor digitorum brevis.

After examining muscle bulk, examine muscle tone in the upper and lower extremities. Instruct the patient to lie still and relax. Move the arms at the elbows and wrists, looking for an increase in resistance. Check tone in the legs while the patient lies flat. Grasp the thigh and lower leg from above and shake the leg, looking for movement at the foot: normally, the foot moves back and forth loosely, but in patients with hypertonicity, the foot remains stiff at the ankle. Abnormalities of tone are divided into:

- Flaccidity which is a floppy decrease in tone that points to a peripheral nervous system lesion or to a hyperacute central nervous system lesion (e.g., an acute stroke or spinal shock).
- Spasticity which is characterized by an initial increased resistance to attempted limb movement which dissipates as joint displacement increases. Spasticity is most obvious when attempting to extend the flexed arm or flexing the extended leg. This is the form of hypertonicity caused by disease of the pyramidal system.

- Rigidity which is an increase in tone independent of the velocity and direction of movement. It is the increase in tone caused by extrapyramidal disease.
- Paratonia which is an increase in tone that varies with the amount of applied resistance. It is caused by frontal lobe pathology.

Power

When examining power, oppose the muscle being tested with a muscle of approximately equal strength. Use extra effort for large, physically fit patients. You will often need to exercise a mechanical advantage to find subtle weakness in muscles such as quadriceps, tibialis anterior, and gastrocnemius, as these muscles tend to be strong when using conventional muscle strength testing techniques. Subtle weakness of gastrocnemius, in fact, may be detected only by a patient's inability to stand on their toes. Genioglossus, abductor digiti minimi, and iliopsoas lie at the other extreme, and you should give these muscles a mechanical advantage to avoid incorrectly labeling them as weak. Be aware of "giveway" weakness caused by pain or poor effort: encourage the patient to push as hard as they can for even as little as 1 second if it appears that they are not giving maximal effort.

While there is no substitute for detailed knowledge of the nerve roots, nerves, and muscles that control joint movement, relearning all the details of first-year medical school anatomy is not necessary to localize the source of weakness for an individual patient. Table 10.1 distills neuromuscular anatomy and testing to 20 commonly tested movements. The muscles are organized into proximal and distal groups, whether they are disproportionately weak in pyramidal (corticospinal) lesions and by the nerve roots and nerves that innervate them. *Aids to the Examination of the Peripheral Nervous System* is an additional, invaluable guide to the sensorimotor examination [1].

Proximal Weakness: History

The proximal muscles are those that are close to the trunk. Complaints of proximal muscle weakness include difficulty when reaching overhead, combing or brushing the hair, rising from a seated position, or ascending stairs. Patients with proximal weakness may describe themselves as "walking like a cowboy" with bowed legs and side-to-side waddling. Contrary to popular belief, proximal weakness is not pathognomonic for myopathic disease. Other localizations that commonly produce proximal weakness include the motor neuron, nerve root, motor nerve, and neuromuscular junction.

Table 10.1 Commonly tested movements

Action	Principal muscle or muscles	Proximal or distal	Disproportionately weak in pyramidal lesion?	Nerve roots	Nerve
Neck flexion	Multiple	Proximal	No		
Neck extension	Multiple	Proximal	No		
Shoulder abduction	Deltoids	Proximal	Yes	C5-6	Axillary
Elbow flexion	Biceps	Proximal	No	C5-6	Musculocutaneous
Elbow extension	Triceps	Proximal	Yes	C6-8	Radial
Wrist flexion	Flexor carpi radialis (FCR), flexor carpi ulnaris (FCU)	Distal	No	C6-7, C8-T1	Median (FCR) and ulnar (FCU)
Wrist extension	Extensor carpi radialis brevis, extensor carpi radialis longus, extensor carpi ulnaris	Distal	Yes	C7	Radial
Extension of fingers at MCP joints	Extensor digitorum communis and extensor indicis	Distal	Yes	C7-8	Radial
Extension of fingers at PIP and DIP joints	Lumbricals	Distal	Yes	C8-T1	Median (digits 2 and 3) and ulnar (digits 4 and 5)
Finger abduction	Abductor digiti minimi, dorsal interossei	Distal	Yes	C8-T1	Ulnar
Thumb abduction	Abductor pollicis brevis	Distal	No	C8-T1	Median
Hip flexion	Iliopsoas	Proximal	Yes	L2-3	Femoral/L2-3 roots
Hip abduction	Gluteus medius and minimus	Proximal	Yes	L5-S1	Superior gluteal
Hip adduction	Adductor longus and magnus	Proximal	No	L2-3	Obturator
Knee flexion	Hamstrings	Proximal	Yes	L5-S1	Sciatic
Knee extension	Quadriceps	Proximal	No	L2-4	Femoral
Foot dorsiflexion	Tibialis anterior	Distal	Yes	L4-5	Peroneal
Foot plantarflexion	Gastrocnemius	Distal	No	S1	Tibial
Toe extension	Extensor hallucis, extensor digitorum	Distal	Yes	L5	Peroneal
Toe flexion	Flexor digitorum	Distal	No	S1	Tibial

MCP metacarpophalangeal, *PIP* proximal interphalangeal, *DIP* distal interphalangeal

Associated Features

Muscle tenderness, usually mild, is a feature of some myopathic disorders; severe pain in myopathy is uncommon. Rhabdomyolysis and myoglobinuria suggest the possibility of a metabolic myopathy or viral myositis. Rash points to dermatomyositis or to an overlap myopathy. Diplopia, ptosis, and dysphagia are seen in patients with myasthenia gravis or oculopharyngeal muscular dystrophy. Dry eyes and dry mouth often accompany Lambert-Eaton myasthenic syndrome. Cramps, fasciculations, and muscle atrophy are features of amyotrophic lateral sclerosis.

Proximal Weakness: Examination

Muscle Bulk

Proximal weakness with prominent muscle atrophy suggests a long-standing muscular dystrophy or cachexia. Most patients with inflammatory myopathies do not have muscle wasting in the early stages. Amyotrophic lateral sclerosis causes reduced muscle bulk but usually produces multifocal rather than proximal weakness. Neuromuscular junction disorders should not affect muscle bulk.

Muscle Strength

Muscle strength testing should always begin with examination of neck flexion and extension, especially for patients with proximal muscle weakness. In most patients, neck flexors become weak before neck extensors. The proximal muscles of the arms include the deltoids, biceps, and triceps. In the legs, the proximal muscles include the iliopsoas, quadriceps, gluteal muscles, and hip adductors.

Exercise Testing

Muscle fatigability is the defining feature of myasthenia gravis. This is most easily assessed at the deltoid. First, test the maximal strength of shoulder abduction. Next instruct the patient to abduct the arm 20–30 times in succession at a frequency of approximately twice per second. Observe for either a failure to complete the series of contractions or a decrease in strength when testing the patient after the final contraction. If necessary, use contralateral shoulder abduction as a control for patients with subtle weakness.

All patients with proximal weakness should also undergo testing for post-exercise facilitation, the characteristic finding of the presynaptic neuromuscular junction disorder Lambert-Eaton myasthenic syndrome. To test for post-exercise facilitation, instruct the patient to contract a weak muscle maximally against

resistance for 10 seconds. Post-exercise facilitation is present if there is a clear improvement in muscle strength after brief exercise.

Reflexes

Patients with myopathies usually have normal deep tendon reflexes unless there is substantial weakness or muscle atrophy. Lambert-Eaton myasthenic syndrome classically causes diminished or absent reflexes that reappear when the reflex is checked after 10 seconds of sustained exercise of the associated muscle (e.g., the patellar reflex will return after exercising the quadriceps). Neuropathic and radiculopathic conditions should produce hyporeflexia or areflexia. Upper motor neuron dysfunction in ALS may produce hyperreflexia, but because ALS is a disease of both the upper and lower motor neurons, it may also cause hyporeflexia.

Sensation

Sensory examination is usually normal in patients with proximal weakness. Exceptions include Lambert-Eaton myasthenic syndrome and neuropathic conditions such as chronic inflammatory demyelinating polyneuropathy, but in both cases, any sensory loss is overshadowed by muscle weakness. Do not assign too much weight to mild distal pinprick loss, as this is often secondary to a pre-existing but trivial polyneuropathy.

Gait

Patients with proximal muscle weakness waddle from side to side due to weakness of hip abduction, the so-called Trendelenburg gait (Chap. 18). To elicit a Trendelenburg sign, observe the patient from behind, and instruct them to stand on one foot. The sign is said to be present on the right when the pelvis droops towards the left side while the patient is standing on the right leg. Patients with proximal muscle weakness require several attempts to rise from a seated position and may be unable to do it at all. This test is even more difficult if the patient attempts to stand when their arms are folded across their chest.

Other Signs and Symptoms

Bulbar weakness may accompany amyotrophic lateral sclerosis and myasthenia gravis, but is not universal in either condition, especially in their early stages. Dysphagia is prominent in oculopharyngeal muscular dystrophy and may also occur in patients with advanced inflammatory myopathies. Diplopia and ptosis in patients with proximal weakness strongly suggest myasthenia gravis and exclude the

possibility of amyotrophic lateral sclerosis. Myotonia is impaired relaxation of a muscle and is the characteristic finding of myotonic dystrophy and myotonia congenita. If myotonia is not immediately obvious when the patient fails to loosen their grip after shaking your hand, then test for percussion myotonia by briskly tapping the tongue, deltoid, wrist extensors, or thenar eminence with a reflex hammer. Myoedema is a mounding of the muscles upon percussion, seen in patients with severe hypothyroidism.

Laboratory Testing in the Patient with Proximal Weakness

Creatine Kinase (CK)

CK catalyzes the conversion of creatine and ATP to phosphocreatine and ADP. Phosphocreatine is the largest phosphate reserve for regenerating ATP during active muscle contraction. When muscle cells are damaged by a myopathic process, the serum CK level increases. Although CK is the most sensitive and specific blood test for myopathy, as many as 1/3 of otherwise normal people have CK levels greater than the commercially defined upper limit of normal of approximately 150 units/liter [2]. False-positive CK elevation leads to many referrals, though it is rare for a patient with asymptomatic hyperCKemia to have a treatable disorder after comprehensive evaluation including muscle biopsy [3].

CK should be elevated in patients with inflammatory myopathy, dystrophinopathy, limb-girdle dystrophy, and hypothyroidism – question these diagnoses if the CK is normal. CK is usually normal in patients with cachectic myopathy, steroid myopathy, and hyperthyroidism. While an elevated CK level is considered synonymous with myopathy, neuromuscular diseases including ALS, Guillain-Barre syndrome, and even benign cramps may all cause modest CK elevations, sometimes up to 1000 units/liter. Heavy exercise, large muscle bulk, and African ancestry may also increase the CK level in the absence of muscle disease.

Aldolase

Aldolase is an important glycolytic enzyme found in the muscle and liver. It may be elevated in patients with muscle disease but usually adds little to the diagnostic evaluation of a patient with suspected myopathy.

Nerve Conduction Studies (NCS) and Electromyography (EMG)

NCS and EMG are often helpful diagnostic studies for patients with weakness secondary to peripheral nervous system dysfunction (Fig. 10.1) [4]. In brief, for patients with proximal and generalized weakness, nerve conduction studies are useful in pinpointing sites of focal nerve compression and differentiating between axonal and

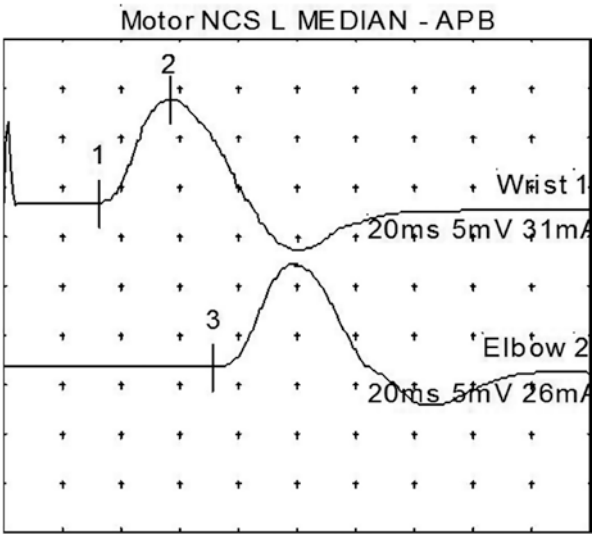

Fig. 10.1 Motor nerve conduction study of the left median nerve recording from the abductor pollicis brevis. The median nerve is stimulated at the wrist (top trace) and at the elbow (bottom trace). Parameters of interest are the distal latency (the time elapsed between stimulation and the onset of the first motor response at point 1), response amplitude (the difference in heights between points 1 and 2), and the conduction velocity (obtained by subtracting the time elapsed between points 3 and 1 and dividing by the distance between the stimulation sites). Axonal neuropathies are characterized by low amplitudes and mildly reduced conduction velocities. Demyelinating neuropathies are characterized by mildly reduced amplitudes and markedly reduced conduction velocities

demyelinating polyneuropathies. Needle EMG helps to localize radiculopathy, detect myopathic processes, and confirm the diagnosis of motor neuron disease. Repetitive nerve stimulation and single-fiber electromyography establish the presence of neuromuscular junction disorders. It is important to recognize the limitations of neurophysiologic testing: as Preston and Shapiro note in their essential textbook on electrodiagnosis, EMG is an extension of the clinical examination, and it is unlikely to establish a specific diagnosis if the diagnosis is not considered prior to performing the test [5].

Muscle Biopsy

Muscle biopsy is routinely performed when a myopathic process is suspected. While a muscle biopsy may help to diagnose many exotic varieties of muscle and nerve disease, it is most important for patients with inflammatory, toxic, or endocrine myopathies because these are potentially treatable conditions. Special histochemical stains and electron microscopy may aid in diagnosis but rarely do these studies increase the likelihood of finding a treatable condition.

Myositis-Associated Antibodies

The diagnosis of an inflammatory myopathy is often difficult: the clinical presentation may be rather nonspecific, CK elevations may not be particularly dramatic, and biopsy may be nondiagnostic. Myositis-associated antibodies are a potentially helpful biomarker in difficult situations. Important autoantibodies include those to Jo-1, signal recognition particle (SRP), and Mi-2. Anti-SRP myopathy is often refractory to corticosteroids and other immunosuppressants. Antibodies to Mi-2 are associated with dermatomyositis, often with fulminant onset.

HMGCR Antibodies

A small group of patients exposed to statins develop a necrotizing myopathy associated with antibodies to HMG-CoA reductase [6, 7]. These patients do not improve upon discontinuation of the statin and require immunomodulatory therapy (see below).

Forearm Exercise Testing

The basis of the forearm exercise test is that muscle contraction leads to the metabolic by-products lactate and ammonia [8]. To perform forearm exercise testing, draw lactate, ammonia, and P_{O2} levels from the antecubital vein. Next, have the patient contract the forearm and hand muscles for 1 minute using a dynamometer. Repeat the blood tests 1, 3, and 5 minutes following exercise. In normal subjects, there is a rise in both lactate and ammonia after exercise, usually to at least twice the resting value. There should also be a reduction in P_{O2} level. In patients with myopathies due to glycolytic enzyme deficiencies, lactate does not rise, but ammonia does. In patients with myoadenylate deaminase deficiency, ammonia rises, but lactate does not. A frustratingly common finding in forearm exercise testing is that both the ammonia and lactate fail to rise sufficiently, reflecting inadequate exercise quality. The characteristic (but infrequent) finding in patients with mitochondrial disease is that there is no reduction in P_{O2} level. Because forearm exercise testing is rarely helpful in establishing a myopathy diagnosis in adults and never uncovers a treatable condition, I perform it only rarely.

Other Laboratory Tests

Panels of genetic tests allow screening for genetic causes of myopathy, particularly the limb-girdle muscular dystrophies and myofibrillar myopathies. Unfortunately, the ease of performing genetic testing, especially whole-exome sequencing, leads to the detection of many "variants of unknown significance" that do not correlate with a patient's symptoms, often in normal patients with asthenia or depression rather than a true myopathic process.

Causes of Proximal and Generalized Weakness

Inflammatory Myopathies

The shared features of the inflammatory myopathies are proximal muscle weakness, creatine kinase elevation, myopathic electromyographic changes, and inflammatory infiltrates on muscle biopsy. Muscle aches and pains, despite common misconception, are not prominent. In adults, inflammatory myopathies are rare but important causes of proximal weakness, as they are often treatable. The four common inflammatory myopathies may be distinguished on clinical as well as pathological grounds.

Polymyositis

Polymyositis is the least common of the three primary inflammatory myopathies. Patients with polymyositis have proximal muscle weakness and elevated creatine kinase. Muscle biopsy shows endomysial lymphocytic infiltrates that invade non-necrotic muscle fibers.

Corticosteroids are the first-line treatment for polymyositis. Prednisone should be initiated at 60–80 mg qd for 2–3 months, after which it is tapered by 5–10 mg each week. Starting prednisone is a serious commitment that requires close monitoring for and prophylaxis against side effects including diabetes, weight gain, cataracts, glaucoma, gastrointestinal ulcers, and accelerated osteoporosis.

A steroid-sparing agent should be added for patients who respond incompletely to steroids or who tolerate them poorly. Methotrexate is usually the agent of first choice. This should be started at 2.5 mg qwk and increased by 2.5 mg qwk to reach a goal of 15–25 mg qwk. Obtain a chest X-ray and pulmonary function tests before starting methotrexate and at least every 6 months to screen for pulmonary fibrosis. Because methotrexate also leads to hepatotoxicity, check liver function tests at least every 2 months. Persistently, elevated liver function tests should prompt referral for liver biopsy.

Azathioprine is usually the next choice among the steroid-sparing agents. Prior to starting this medication, check for TPMT enzyme activity in the blood: patients with reduced TPMT activity are at increased risk for myelosuppression. Start azathioprine at 50 mg per day and titrate up by 50 mg each week to a dose of 1–2 mg/kg over 2–3 weeks. Monitor complete blood counts and liver function tests frequently during the course of therapy.

Some patients with polymyositis with disease refractory to steroids, methotrexate, and azathioprine benefit from treatment with monthly intravenous immunoglobulin infusions.

Dermatomyositis

Dermatomyositis is the most common of the idiopathic inflammatory myopathies. In addition to proximal muscle weakness, patients with dermatomyositis have several characteristic skin changes [9]. The heliotrope rash is a symmetric violaceous mask around the upper and lower borders of the eyes. Gottron papules are elevated violaceous plaques which involve bony prominences, most typically the

metacarpophalangeal and interphalangeal joints. Two other typical skin changes are the V sign (erythema over the anterior neck and chest) and the shawl sign (erythema over the posterior neck and shoulders). Unlike polymyositis and inclusion body myositis, dermatomyositis is a multisystem disorder which often involves the gastrointestinal and pulmonary systems in addition to the skin and skeletal muscle. CK is elevated in the overwhelming majority of patients with dermatomyositis. Muscle biopsy shows perimysial lymphocytic inflammation and perifascicular atrophy. Approximately 25% of patients with dermatomyositis have an underlying malignancy and are at greater risk for developing a malignancy both before and after the diagnosis is made [9]. Patients with dermatomyositis should therefore undergo annual screening for age- and gender-appropriate malignancies. Treat dermatomyositis using an approach similar to that described for polymyositis.

Inclusion Body Myositis (IBM)

IBM is distinguished from other inflammatory myopathies by early involvement of wrist flexors, finger flexors, and quadriceps. CK may be elevated more modestly in IBM than in the other inflammatory myopathies. Diagnostic muscle biopsy abnormalities include endomysial inflammation, rimmed vacuoles, and inclusions within muscle fibers. Unfortunately, IBM does not respond to treatment with corticosteroids or other immunosuppressants. It is slowly progressive over many years.

Overlap Myopathies

Overlap myopathies are inflammatory myopathies that occur in the context of a rheumatologic disorder such as systemic lupus erythematosus, scleroderma, or rheumatoid arthritis. The diagnosis may be a challenging one to make as patients with overlap myopathies have rheumatologic abnormalities that preclude accurate muscle power assessment. Like PM and DM, overlap myopathies are usually steroid responsive.

Muscular Dystrophies

Dystrophinopathies

Duchenne muscular dystrophy (DMD) is an X-linked disorder produced by an out-of-frame mutation in the gene that encodes the muscle membrane protein dystrophin. DMD is always diagnosed in childhood, and survival past early adulthood is not typical. Milder dystrophinopathies, however, may present for the first time in one of several ways in adulthood. Becker muscular dystrophy (BMD) is produced by an in-frame mutation in the dystrophin gene and leads to proximal weakness, sometimes affecting the quadriceps in isolation [10]. Female carriers of the dystrophin mutation may also present with proximal weakness in adulthood [11]. Molecular diagnosis is available to confirm suspected dystrophinopathies. Treatment of dystrophinopathies in adults is mainly supportive. Gene therapy is an area of active investigation.

Limb-Girdle Muscular Dystrophies

Limb-girdle muscular dystrophies (LGMD) are a rare group of disorders which share hip and shoulder muscle weakness as a clinical feature. There are more than 30 forms of LGMD, inherited in both autosomal dominant and recessive forms. Some forms present in early childhood, while others might not be identified until early or mid-adulthood. Many of the mutations that produce LGMD also produce other myopathies. For example, mutations in dysferlin (LGMD 2B) produce distal weakness that is most severe in the calves, and mutations in lamin A/C (LGMD 1B) produce Emery-Dreifuss syndrome, a myopathy with prominent early contractures and cardiomyopathy. The diagnosis of the syndromes with the limb-girdle weakness phenotype is quite challenging because there are usually few distinguishing clues [12]. Genetic testing panels make differentiation of the various forms of LGMD much easier. At present, no specific effective treatments for the LGMD syndromes are available.

Thyroid Myopathies

Myopathies due to hypothyroidism and hyperthyroidism are rare because recognition of thyroid disease usually occurs before muscle pathology has a chance to develop. CK levels are usually elevated in patients with hypothyroid myopathy and normal or mildly elevated in patients with hyperthyroid myopathy. In patients with no other explanation for myopathy, checking thyroid function studies may help to establish a diagnosis. Minor abnormalities should be interpreted cautiously, as they are not likely to be the explanation for a myopathy.

Toxic and Iatrogenic Myopathies

The most important medications and toxins that lead to myopathy are statins, ethanol, and corticosteroids. Other important, though less common, iatrogenic causes are chloroquine, colchicine, hydroxychloroquine, penicillamine, and zidovudine.

Statin-Induced Myopathy

HMG-CoA reductase inhibitors (statins) are commonly prescribed cholesterol-lowering agents that produce muscle pathology including asymptomatic CK elevation, mild muscle aches and cramps, frank myopathy, and rhabdomyolysis [13]. The common statins including atorvastatin, fluvastatin, pravastatin, and simvastatin are all equally likely to lead to myopathy [14]. It should not be assumed that a statin is the cause of proximal weakness in a patient who happens to be taking one of these medications: thorough evaluation for other causes of proximal weakness should be conducted before assigning blame to the statin. The best treatment for muscle problems in patients taking statins is not entirely clear. For patients with tolerable muscle aches or asymptomatic CK elevations, it is usually advisable to continue the statin if it is needed for cardiovascular health. For patients with rhabdomyolysis,

discontinue the statin immediately, and avoid prescribing statins in the future. Alternative lipid-lowering agents including ezetimibe, gemfibrozil, or niacin may also produce myopathic side effects similar to those produced by the statins.

Less commonly, statins may cause an immune-mediated necrotizing myopathy with antibodies to HMG-CoA reductase [6, 7]. This myopathy typically progresses even after the statin is discontinued and requires immunosuppressive treatment similar to that employed for polymyositis.

Alcohol-Related Myopathies

Excessive alcohol use causes two types of myopathy. The first type is an acute-onset myopathy with severe muscle weakness, cramps, and myalgias. The second type is caused by chronic heavy alcohol consumption and is characterized by painless proximal muscle weakness that develops over weeks to months. The exact lifetime dose of alcohol necessary to produce this myopathy and the role of nutritional deficiencies are unclear. Moderate alcohol use (one or two drinks per day) is not sufficient to cause a myopathy. Discontinuing alcohol use may improve symptoms of chronic alcoholic myopathy.

Steroid Myopathy

Chronic, systemic corticosteroid use may lead to a myopathy. At least 4 weeks of steroids are required before a myopathy develops. In many cases, patients have used steroids for years before a myopathy is seen. Fluorinated steroids including dexamethasone, betamethasone, and triamcinolone are more likely than prednisone to lead to myopathy. The typical clinical picture is painless proximal muscle weakness that is greater in the legs than in the arms, mild or no CK elevation, and normal EMG. Other features of chronic steroid use are often present. In most patients, the chronology of steroid administration and symptom development makes diagnosis straightforward. For patients who receive steroids for inflammatory myopathy or myasthenia gravis, establishing whether the problem is steroid myopathy or the condition for which the steroids are being prescribed may be more challenging. Muscle biopsy demonstrating type II muscle fiber atrophy may be necessary to confirm a steroid myopathy for these patients. Symptoms usually improve several weeks to months after steroid discontinuation. Physical activity may help to prevent steroid myopathy.

Other Myopathies

Almost all treatable myopathies are due to inflammatory, iatrogenic, toxic, or endocrine processes.

Two uncommon myopathies deserve mention because they may be treatable. Acid maltase deficiency is a metabolic myopathy characterized by proximal weakness and prominent respiratory failure that may respond to infusions of alpha-glucosidase [15]. Mitochondrial myopathy is often part of a multisystem disorder requiring muscle biopsy and genetic analysis and is usually treated with a cocktail

containing vitamin E, creatine monohydrate, and coenzyme Q10 with variable results. Other dystrophic and metabolic myopathies are usually not treatable, and the length to which a diagnosis is pursued is largely determined by the patient's desire for an explanation rather than an expectation of improvement.

Generalized Myasthenia Gravis

Myasthenia gravis is an autoimmune disease produced by antibodies that disrupt function of the postsynaptic neuromuscular junction. Although many patients develop fixed weakness, fatigability with exercise is the distinguishing feature of myasthenia gravis. Generalized myasthenia gravis refers to myasthenia gravis that affects proximal skeletal muscles. Other common forms of myasthenia gravis include ocular myasthenia (Chap. 6), myasthenic crisis (Chap. 12), and bulbar myasthenia (Chap. 8). Patients with generalized myasthenia gravis usually, but not always, have preceding or accompanying ocular signs and symptoms. In their absence, the diagnosis may be challenging.

The two bedside tests that may be used to confirm a diagnosis of myasthenia gravis are the ice test and the edrophonium or Tensilon test, both of which are described in more details in Chap. 6, as they are more reliable in patients with ocular symptoms than in patients with isolated proximal muscle weakness.

The diagnosis of myasthenia gravis is most often established by finding acetylcholine receptor (AChR) binding antibodies in the blood. A very small minority of patients without AChR binding antibodies have blocking or modulating antibodies. Of the 20% of myasthenics without AChR antibodies, half possess antibodies to muscle-specific tyrosine kinase (MuSK) and a smaller percentage to lipoprotein receptor-related protein 4 (LRP4) antibodies [16, 17]. Patients with no detectable antibodies are called seronegative myasthenics and require electrophysiologic testing to establish the diagnosis. The characteristic finding is the electrodecremental response to 3-Hz repetitive nerve stimulation (RNS) (Fig. 10.2). If RNS is normal, single-fiber electromyography (SFEMG) showing abnormal jitter and blocking may help to establish the diagnosis. All patients with myasthenia gravis should undergo a CT scan of the chest to look for thymoma or thymic hyperplasia.

While symptomatic treatment with the acetylcholinesterase inhibitor pyridostigmine may improve symptoms of ocular myasthenia, it is not usually an effective treatment strategy for generalized myasthenia gravis. Almost all patients with generalized myasthenia gravis require immunosuppression with corticosteroids. Rapid steroid initiation, however, is often harmful to myasthenics, exacerbating their symptoms and sometimes leading to myasthenic crisis [18]. A safer approach for patients with generalized myasthenia is to start prednisone at a dose of 10 mg and to titrate upwards to a goal of 60–80 mg per day over 4–6 weeks. The daily dose can be tapered by 5–10 mg each week after 6–8 weeks of high-dose treatment. Benefit from starting or increasing steroids in myasthenia gravis is typically seen first at

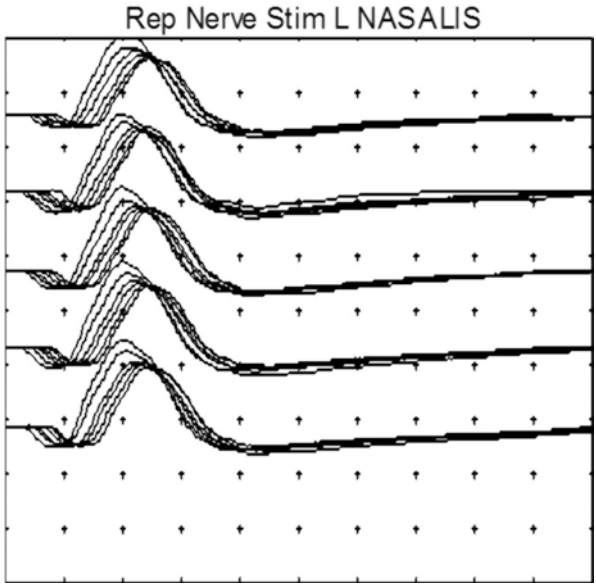

Fig. 10.2 Slow (3-Hz) repetitive nerve stimulation of the left facial nerve recording nasalis. Six recordings are present in each of the five traces. Note the electrodecremental response suggestive of a disorder of neuromuscular transmission

2 weeks and reaches a maximum at 1 or 2 months. In many cases, steroids by themselves are inadequate for the treatment of myasthenia gravis, and additional immunosuppressive agents such as mycophenolate mofetil (500 mg bid, titrated up to 1500 mg bid as needed) or azathioprine (50 mg qd, titrated up by 50 mg qd per week to a goal dose of 1–2 mg/kg qd) are needed. Mycophenolate mofetil and azathioprine may not provide any benefit, however, until 3–6 months (or longer) after they are started.

Patients with thymoma should undergo thymectomy, usually within several weeks to months of discovery if there is evidence of malignant invasion. Even patients with non-thymomatous myasthenia gravis may benefit from thymectomy [19]. It should not be offered routinely to patients with myasthenia gravis with MuSK antibodies, as it is less effective for this patient group [20]. In order to optimize the perioperative course, thymectomy should be performed when symptoms are relatively stable and the daily dose of prednisone is 20 mg or less. I pre-treat patients with unstable myasthenia gravis with five infusions of IVIg or five plasma exchanges ending approximately 1 week before anticipated thymectomy.

Lambert-Eaton Myasthenic Syndrome (LEMS)

LEMS is a disorder of neuromuscular transmission produced by antibodies to presynaptic voltage-gated calcium channels. It occurs classically in middle-aged people with underlying neoplasms, most commonly small cell lung cancer. Almost as frequently, LEMS is secondary to a nonneoplastic autoimmune disorder and may be accompanied by rheumatoid arthritis, pernicious anemia, or hypothyroidism. The typical presentation of LEMS is subacute-to-chronic proximal weakness which is

greater in the legs than in the arms. It may be associated with fatigability but, in many cases, resembles a myopathy in that the symptoms do not fluctuate. Some patients have bulbar and extraocular muscle weakness, but the diagnosis is unlikely if these are the most prominent or sole clinical features. Because voltage-gated calcium channels are also present on sensory and autonomic nerve terminals, patients with LEMS may also have mild sensory symptoms and autonomic dysfunction including dry mouth, constipation, and orthostatic hypotension. The cardinal examination finding in patients with LEMS is post-exercise facilitation of strength and reflexes.

Confirm the diagnosis of LEMS by checking the blood for antibodies to voltage-gated calcium channels. For patients who require more rapid diagnosis (antibody results usually return after 1–2 weeks), the characteristic electrophysiologic finding is reduced compound muscle action potential amplitude that increases after 10 seconds of sustained exercise (Fig. 10.3). Because small cell lung cancer and LEMS coexist so commonly, order a CT scan of the chest for all patients. Screen for other cancers as indicated by demographic risk factors and physical examination. If there is no evidence for a tumor or autoimmune disorder, repeat the surveillance scans every 3–6 months, as LEMS may predate cancer diagnosis by several years.

Treating LEMS is usually challenging. Addressing the underlying cancer or autoimmune disease is the first step. Patients may show a modest response to the acetylcholinesterase inhibitor pyridostigmine at a dose of 60 mg qid. The potassium channel blocker 3,4-diaminopyridine is also modestly effective. Patients with longer life expectancies (usually those with non-paraneoplastic LEMS) often require steroids, intravenous immunoglobulin, or other immunosuppressants.

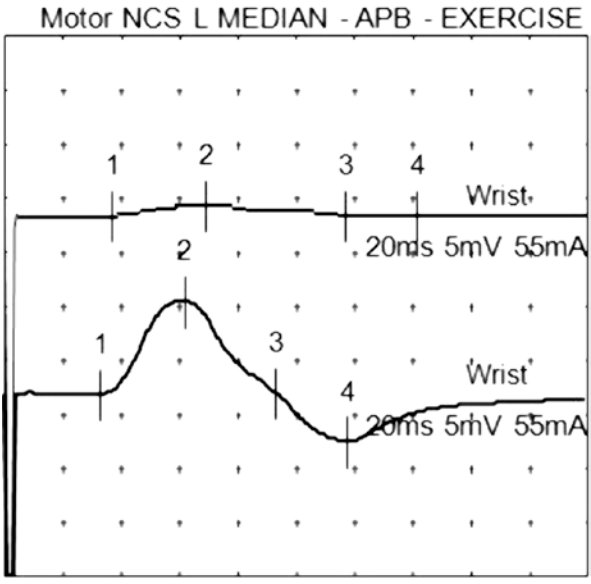

Fig. 10.3 Motor nerve conduction study obtained by stimulating the left median nerve and recording the left abductor pollicis brevis in a patient with Lambert-Eaton myasthenic syndrome at rest (top trace). Ten seconds of sustained exercise followed by another stimulation produces an incremental response using the same recording parameters (bottom trace)

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

As its name indicates, CIDP is an immune-mediated polyradiculoneuropathy that develops over several months. Weakness in CIDP is both proximal and distal, is symmetric, and is accompanied by hyporeflexia or areflexia. Sensory deficits are usually present but overshadowed by motor abnormalities. Be skeptical about any patient referred with a diagnosis of CIDP, as it is overdiagnosed [21].

Nerve conduction studies demonstrate changes consistent with demyelination including markedly slow nerve conduction velocities, abnormal temporal dispersion, and conduction block (Fig. 10.4). Similar to Guillain-Barre syndrome (Chap. 12), the CSF in CIDP shows albuminocytologic dissociation in which an elevated protein is unaccompanied by an elevation in white blood cell count. HIV, Lyme disease, sarcoidosis, and lymphoma or leukemia should be considered for patients with a CIDP-type presentation and more than ten white blood cells/mm^3 in the CSF.

While CIDP is usually idiopathic, it may be associated with systemic diseases, the most widely known of which are HIV infection and osteosclerotic myeloma. Patients with osteosclerotic myeloma develop the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) [22]. First steps in evaluating for the possibility of myeloma include serum protein electrophoresis, urine protein electrophoresis, immunofixation, calcium levels, and a skeletal survey to evaluate for a possible myeloma.

Corticosteroids and intravenous immunoglobulin (IVIg) are the two agents that are most effective for patients with CIDP. Because IVIg causes fewer side effects, it is usually the treatment of first choice. Initiate IVIg at 0.4 mg/kg/day for 5 days, and

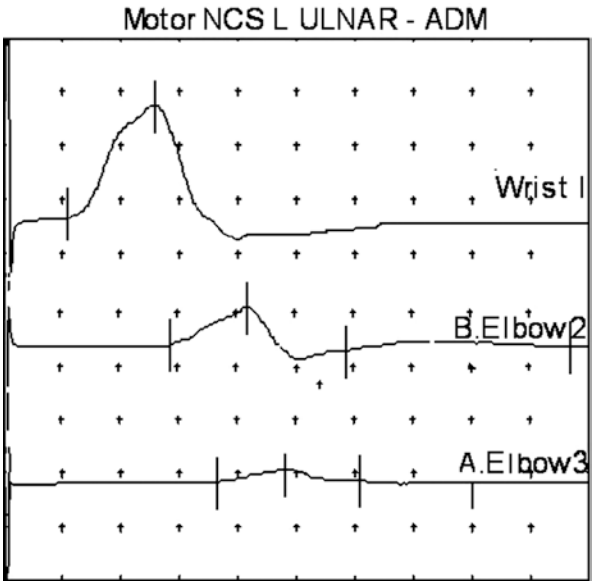

Fig. 10.4 Motor nerve conduction study of the left ulnar nerve recording abductor digiti minimi. Note the drop in amplitude (measured from the baseline to the peak) with stimulation at the above and below elbow sites as compared to the amplitude obtained by stimulating at the wrist. This is conduction block, a pathognomonic finding of inherited demyelinating neuropathies such as Guillain-Barre syndrome and chronic inflammatory demyelinating polyneuropathy

follow with monthly supplemental doses of 0.4–1 mg/kg. For patients who do not respond to IVIg, start prednisone at a dose of 60 mg, and taper by 5–10 mg per dose per week. Although most patients will benefit from IVIg or prednisone, CIDP is a relapsing disease that tends to worsen when treatment is withdrawn.

Amyotrophic Lateral Sclerosis (ALS)

ALS is a degenerative disease of motor neurons characterized by progressive muscle wasting and weakness. Although people of any age may develop ALS, the typical patient is in their 50s or 60s and presents initially with hand clumsiness, gait difficulty, or dysphagia. Patients may not complain specifically of weakness. In the earliest stages, symptoms are quite subtle and may be overlooked or assigned to more common conditions such as radiculopathy, compression mononeuropathies, or musculoskeletal disorders. Because essentially any subacute-to-chronic onset focal-or-generalized pattern of weakness described in this or the next chapter may be secondary to ALS, it is important to always consider the diagnosis in patients with painless muscle weakness.

The findings in ALS are best explained with reference to the motor neuron pool. The upper motor neurons originate in the cerebral cortex and descend through the corticospinal tract, while the lower motor neurons originate in the anterior horn cell in the spinal cord. ALS causes degeneration of both upper and lower motor neurons, although lower motor neuron symptoms including multifocal weakness, wasting, and fasciculations often predominate in the initial stages of the disease. While fasciculations are a well-known finding in ALS, they are not pathognomonic for the diagnosis, and their absence does not exclude ALS. Upper motor neuron findings include dysarthria, spasticity, and hyperreflexia. Sphincter function and extraocular movements are unimpaired. Sensation should be preserved. On the surface, cognition is preserved, but most patients eventually show signs of frontal dysfunction if they are tested carefully enough. In some, this frontal dysfunction is the main source of disability and may be severe enough to lead to nursing home placement. Variants of ALS include progressive muscular atrophy in which exclusively lower motor neuron findings are present and primary lateral sclerosis in which exclusively upper motor neuron findings are present. These variants are associated with better long-term prognoses than ALS, although both lead to disability and ultimately to death.

Patients with suspected ALS should undergo EMG: fibrillations, positive sharp waves, and large motor units establish more widespread lower motor neuron involvement than may be evident from bedside examination. EMG also helps to distinguish ALS from multifocal motor neuropathy with conduction block, the condition that most frequently mimics it (Chap. 11). MRI of the brain and spine should be performed to exclude structural processes which may lead to weakness and wasting.

Unfortunately, ALS is a relentlessly progressive condition that leaves patients paralyzed, unable to speak, eat, or breathe and confined to bed requiring 24-hour care. Patients ultimately die of respiratory failure unless they are among the small minority who choose long-term mechanical ventilation. There are two medications

approved as disease-modifying agents for the treatment of ALS. The glutamate antagonist riluzole (50 mg bid) is marginally effective at prolonging lifespan and has an unclear benefit on delaying functional decline [23]. Edaravone is an infusion that is given to selected ALS patients in monthly cycles and may help with function but does not provide any survival benefit [24]. Noninvasive positive pressure ventilation is an important intervention that increases lifespan in ALS patients [25]. Care is largely supportive and involves a multidisciplinary team of physical and occupational therapists, speech and swallowing specialists, social workers, and nutritionists.

Central Nervous System Dysfunction

Peripheral nervous system disease accounts for most cases of proximal muscle weakness. The classic example of central nervous system dysfunction that breaks this rule is infarction in the borderzone or watershed between the anterior and middle cerebral arteries (Chap. 21). Cervical spine disease (Chap. 17) may also lead to predominantly proximal weakness of both arms and legs, often without much sensory dysfunction.

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Focal Limb Weakness

11

Anatomy

Asymmetric limb weakness generally conforms to one of several common patterns (Table 11.1). Mastering the three to five most common causes of each pattern is a powerful clinical tool which will help in localizing and diagnosing most patients with focal limb weakness. However, any pattern-matching algorithm has limitations, and a firm grounding in the anatomy of the motor system (see also Chap. 10) becomes necessary when evaluating patients with asymmetric weakness, especially for those patients with atypical, multifocal, and traumatic deficits.

The motor pathways that control the extremities begin in the precentral gyrus of the contralateral motor cortex (Fig. 11.1). Motor neurons controlling the leg are located medially within the cortex while those controlling the arm are found superiorly and laterally. From the cortex, motor fibers descend through the subcortical white matter and the posterior limb of the internal capsule. The motor pathways continue in the cerebral peduncle and then in the ventral pons, crossing within the

Table 11.1 Patterns of focal limb weakness

Location of weakness	Most common sites of pathology
Shoulder	C5–C6 nerve roots, upper trunk of brachial plexus
Periscapular region	Long thoracic nerve, spinal accessory nerve
Intrinsic hand muscles	Ulnar nerve, anterior horn cells, cerebral cortex
Wrist drop	Radial nerve, cerebral cortex
Hip and proximal leg	L2–L3 nerve roots, lumbosacral plexus, femoral nerve, obturator nerve
Foot drop	Peroneal nerve, sciatic nerve, L5 nerve root, anterior horn cells, cerebral cortex
Hemiparesis	Cerebral cortex, subcortical white matter, internal capsule
Multifocal	White matter of the brain and spine, multiple nerve roots, multiple nerves, anterior horn cells

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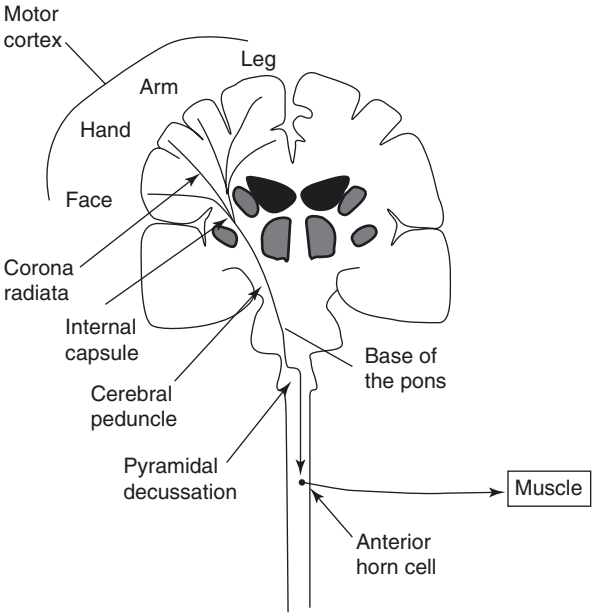

Fig. 11.1 Schematic of the motor system

pyramids of the medulla. Motor fibers descend predominantly through the lateral corticospinal tract to reach the anterior horn cells. The nerve roots are derived from the anterior horn cells and form the brachial or lumbosacral plexi which give rise to the named nerves. These nerves innervate the muscles via the neuromuscular junctions. Although focal weakness may be derived from any of these structures, problems at the level of the neuromuscular junction and the muscles usually lead to generalized rather than focal weakness of the extremities.

Shoulder Weakness

C5–C6 Radiculopathy

Pain and paresthesias are usually the most prominent symptoms of cervical radiculopathy. C5–C6 radiculopathy may produce weakness of arm abduction, arm flexion, and external rotation, but there is substantial overlap among adjacent myotomes, and weakness secondary to radiculopathy is often subtle. Biceps and brachioradialis reflexes may be diminished or lost. Sensation is decreased over the lateral shoulder and arm. Patients with C5–C6 radiculopathy substantial enough to produce weakness should undergo evaluation and treatment as discussed in Chap. 17.

Brachial Plexopathy

It is important to maintain a healthy skepticism when considering the possibility of a brachial plexopathy, as lesions of the plexus are rare in comparison to

radiculopathy and musculoskeletal conditions such as rotator cuff tendonitis. Brachial plexus lesions occur most commonly in the setting of trauma, cancer, and idiopathic brachial neuritis. They are usually quite painful, and for this reason, they are discussed in more detail in Chap. 16. Although memorizing the structure of the brachial plexus is among the most time-consuming tasks in learning neuroanatomy, detailed anatomic knowledge is often not necessary because most plexus lesions conform to one of the three common patterns:

Upper trunk brachial plexopathy produces proximal arm weakness involving the suprascapular (infraspinatus/external rotation), axillary (deltoid/shoulder abduction), and musculocutaneous (biceps/elbow flexion) nerves. It is often difficult to distinguish weakness due to an upper trunk lesion from a C5 to C6 radiculopathy: both imaging and electrophysiologic studies are often necessary. Sensory signs and symptoms involve the lateral shoulder, arm, forearm, and hand.

Lower trunk brachial plexopathy produces weakness of the hand muscles and sensory symptoms involving the medial hand, forearm, and arm. Patients with lower trunk plexopathies often have accompanying Horner syndrome (Chap. 6).

Pan-plexopathy produces widespread weakness and sensory disturbances in the upper extremity. It is among the most common patterns of plexus lesions, especially in the context of trauma or neoplastic infiltration.

Periscapular Weakness (Scapular Winging)

Long Thoracic Neuropathy

The long thoracic nerve innervates the serratus anterior which stabilizes the scapula. A lesion of this nerve leads to medial scapular winging. This can be elicited on physical examination by examining the patient from behind while they attempt to do a push-up against a wall with their arms adducted to their trunk. The medial border of the scapula will elevate away from the posterior thoracic wall. Long thoracic neuropathy may occur as a mononeuropathy, classically in a patient who has just undergone thoracotomy. It also occurs in conditions as part of brachial plexopathy, as in idiopathic brachial neuritis.

Spinal Accessory Neuropathy

The other common cause of asymmetric scapular winging is spinal accessory neuropathy. This scapular winging is characterized by lifting of the superolateral border of the scapula away from the posterior thoracic wall upon attempted abduction and external rotation of the arm. In addition to scapular winging, spinal accessory neuropathy produces weakness of ipsilateral shoulder shrug (trapezius) and contralateral head turning (sternocleidomastoid). The spinal accessory nerve may be entrapped at the jugular foramen (in which case the glossopharyngeal and vagus nerves will also be involved, as discussed in Chap. 8) and the posterior cervical triangle. More commonly, though, the spinal accessory nerve is injured during cervical lymph node dissection.

Hand and Finger Weakness

Ulnar Neuropathy

The ulnar nerve innervates most of the intrinsic hand muscles and is therefore the mononeuropathy most likely to lead to hand muscle weakness. The usual cause of ulnar neuropathy is compression of the nerve at the elbow, a site at which it is relatively exposed to wear-and-tear trauma. Less common sites of ulnar nerve damage are the forearm (especially in patients with diabetes) [1] and at the wrist in cyclists or in heavy older patients who rest their weight on their wrists while using walkers. Numbness and paresthesias are usually present in the fourth and fifth digits, but in some cases, sensory complaints are completely absent. In severe cases, there may be atrophy of the hypothenar eminence and first dorsal interosseous (the fleshy muscle between the thumb and index finger). Weakness of abduction of digits two and five is appropriately tested by applying finger pressure from the sides and not by forcefully squeezing the fingers together. Flexion of the distal interphalangeal joints of digits four and five may be weak. Sensory loss is classically noted in the fifth digit and in the ulnar half of the fourth digit on both the palmar and dorsal aspects of the hand. Confirm the localization of a suspected ulnar neuropathy with nerve conduction studies. Mild ulnar neuropathies may respond to conservative measures such as wearing an elbow pad. More severe ones, particularly those that produce prominent weakness, are likely to require surgical release and transposition of the ulnar nerve.

Motor Neuron Disease

Focal hand weakness and wasting are often the first symptoms of amyotrophic lateral sclerosis, a disorder discussed in more detail in Chap. 10.

C8–T1 Radiculopathy

A C8 or T1 radiculopathy may produce focal hand weakness, usually in association with neck pain and paresthesias radiating into the arm and hand. In general, the C8 and T1 nerve roots are relatively protected from degenerative spine disease, making this a relatively uncommon cause of hand weakness.

Cerebral Causes of Hand Weakness

Two common stroke syndromes lead to prominent hand weakness. The first is infarction of the contralateral motor cortex (the “hand knob”) which produces weakness resembling an ulnar or radial neuropathy [2]. The second is the dysarthria-clumsy hand syndrome which results from lacunar infarction in the subcortical white matter, internal capsule, or pons [3]. Contralateral cerebral cortical or

subcortical lesions such as neoplasms, abscesses, or demyelinating lesions may also produce hand weakness.

Wrist and Finger Drop

Wrist and finger drop are special kinds of hand weakness that develop acutely and are characterized by weakness of extension at the wrist and fingers. The most common causes of wrist and finger drop are stroke and radial neuropathy.

Stroke

Branch middle cerebral artery infarction is the most common cause of hand and arm weakness secondary to stroke. Because the cortical representations of the hand and face are adjacent to each other in the motor homunculus, hand weakness is often (but not always) accompanied by facial weakness.

Radial Neuropathy

Saturday night palsy is the classic radial neuropathy: an intoxicated patient, after a night of heavy sleep with their arm draped over a chair, awakens and finds that they cannot extend the wrist or fingers. Intoxication is not a prerequisite for Saturday night palsy, and it may develop in any state of prolonged immobilization such as surgery or even normal deep sleep. Other common etiologies of radial neuropathy include vasculitis related to mononeuropathy multiplex and multifocal motor neuropathy with conduction block (see below).

Differentiating Between Stroke and Radial Neuropathy

The following examination techniques help to distinguish between a stroke and a radial neuropathy:

1. Most compressive radial neuropathies occur at the level of the spiral groove, distal to the branches that innervate triceps. Thus, a patient with a compressive radial neuropathy usually has profound weakness of wrist and finger extension with preserved arm extension. A patient with a stroke may have triceps or upper arm weakness in addition to wrist drop.
2. Testing extension of the interphalangeal joints may also help to differentiate between the two localizations. The prime extensors at these joints are the lumbricals which are innervated by the median (digits 2 and 3) and ulnar (digits 4 and 5) nerves. Thus, extension of the interphalangeal joints should be preserved in a patient with an isolated radial neuropathy but may be weak in a patient with a stroke.

3. The pattern of sensory loss in the hand is also helpful in differentiating a radial neuropathy from a stroke. In a patient with radial neuropathy, sensory loss affects the dorsal hand, while in stroke sensory loss is typically greater in the palm.

Should any difficulty remain in distinguishing between a stroke and a radial neuropathy, brain MRI with diffusion-weighted imaging to evaluate for stroke or EMG to investigate for radial neuropathy should be performed.

Hip and Proximal Leg Weakness

L2–L3 Radiculopathy

Spinal stenosis commonly involves the L2 or L3 nerve roots in older adults. Pain and paresthesias radiating from the back into the hip and thigh are usually more prominent in patients with upper lumbar radiculopathies, but in some cases, proximal leg weakness is the chief complaint. Because spinal stenosis is such a common radiologic finding in older patients, it is often difficult to determine whether it is the true cause of weakness or if it is only an incidental finding. Upper lumbar radiculopathy is discussed in greater detail in Chaps. 16 and 17.

Lumbosacral Plexopathy

Like brachial plexopathy, lumbosacral plexopathy is usually associated with exquisite pain and is therefore discussed in greater detail in Chap. 16. Common causes of lumbosacral plexopathy include trauma, neoplastic infiltration, diabetic amyotrophy, and retroperitoneal hematoma.

Foot Drop

Weakness of tibialis anterior, the principal dorsiflexor of the foot, results in foot drop. From distal to proximal, possible responsible lesion sites include the peroneal nerve, sciatic nerve, lumbosacral plexus, L4–L5 nerve roots, and the corticospinal tract. In most cases, the cause is in the peripheral nervous system, and the localization of foot drop is determined by the presence or absence of weakness of other lower extremity muscles (Table 11.2).

Peroneal Neuropathy

Peroneal nerve damage results in weakness of foot dorsiflexion and eversion. An important caveat is that foot inversion (mediated by the tibial nerve and tibialis posterior) often appears to be weak when dorsiflexion weakness is severe: to properly test for inversion weakness in patients with severe dorsiflexion weakness, the foot must be passively dorsiflexed. Doing so in a patient with peroneal neuropathy

Table 11.2 Distinguishing among peripheral nervous system sources of foot drop

	Dorsiflexion, tibialis anterior	Eversion, peroneus longus	Inversion, tibialis posterior	Plantarflexion, gastrocnemius	Hip abduction, gluteus medius
Peroneal nerve	+	+	–	–	–
Sciatic nerve	+	+	+	+	–
L5 radiculopathy	+	+	+	–	+

will make the relative preservation of inversion compared to eversion strength obvious. Damage to the peroneal nerve usually occurs as a result of trauma or prolonged immobilization. Sometimes, there is no clear precipitant. In patients without a relevant history of trauma, consider the possibilities of mononeuropathy multiplex and multifocal motor neuropathy with conduction block.

Sciatic Neuropathy

The sciatic nerve divides into the common peroneal and tibial nerves at the knee. A sciatic nerve lesion proximal to this division, therefore, should produce weakness of dorsiflexion, plantarflexion, foot inversion, and foot eversion. Many cases of sciatic neuropathy, however, preferentially involve the peroneal fascicles while sparing the tibial fascicles. In such cases, a sciatic neuropathy may only be distinguishable from a peroneal neuropathy electromyographically. The etiologies of sciatic neuropathy include trauma, immobilization, mononeuropathy multiplex, and multifocal motor neuropathy with conduction block.

L5 Radiculopathy

Most L5 radiculopathies that produce foot drop are associated with lower back pain. The pattern of motor abnormalities help to distinguish L5 radiculopathy from peroneal or sciatic neuropathy when pain is absent: an L5 radiculopathy would be expected to produce weakness of dorsiflexion, inversion, eversion, and hip abduction while sparing plantarflexion. L5 radiculopathy should be confirmed with MRI of the lumbosacral spine. Strongly consider surgery for patients with structural disc disease severe enough to produce a foot drop.

Motor Neuron Disease

Isolated foot drop may be the first abnormality in ALS. Careful examination may disclose other muscle weakness, muscle atrophy, and fasciculations which support the diagnosis. Electromyography demonstrating denervation in multiple myotomal levels will help to confirm the diagnosis.

Central Nervous System Localizations

While more widespread lower extremity weakness might be expected with central nervous system disease, medial frontal lesions may also produce isolated or predominant foot drop. Foot weakness may be an isolated deficit, but helpful neighborhood clues to a central nervous system source include the presence of headache, abulia, or transcortical motor aphasia (Chaps. 3 and 4). Anterior cerebral artery stroke, dural sinus thrombosis, tumor, and hemorrhage are among the most common central nervous system etiologies of foot drop.

Treating Foot Drop

Treatment of foot drop begins by addressing the underlying cause. Physical therapy and wearing an ankle foot orthosis to keep the foot passively dorsiflexed while the patient recovers is helpful regardless of the cause. It is important to counsel patients on the prolonged (up to 2 years) and sometimes incomplete recovery from foot drop due to severe peripheral nerve lesions. EMG is often helpful for prognostication.

Postpartum Leg Weakness

Leg weakness following delivery occurs in approximately 1% of women [4]. The etiologies are usually benign and self-resolving, but some are more serious:

- Femoral neuropathy is secondary to excessive thigh abduction and external rotation during delivery. It produces weakness of hip flexion and knee extension with sensory loss in the anterior thigh and medial leg.
- Obturator neuropathy is usually the result of compression of the obturator nerve by the baby during descent through the pelvis. Clinical features are weakness of thigh adduction and sensory loss in the medial thigh. Risk factors for obturator nerve compression include prolonged labor and cephalopelvic disproportion.
- Lumbosacral plexopathy is also caused by the descent of the baby through the pelvis. Due to the positioning of the component nerves within the pelvis, the peroneal nerve is often affected out of proportion to the other nerves of the lumbosacral plexus.
- Peroneal neuropathy may be produced by nerve compression within the pelvis or by compression of the fibular neck against stirrups during delivery.
- Conus medullaris and cauda equina syndromes (Chap. 17) are exceedingly rare complications of epidural anesthesia. Because many women have back pain after delivery, new neurologic deficits are often ascribed to the injection. Careful neurologic examination, and in some cases imaging of the lumbosacral spine, however, discloses that procedure-related lesions of the conus medullaris or cauda equina are almost never responsible.

- Central nervous system processes, particularly superior sagittal venous sinus thrombosis, are rare but important causes of postpartum leg weakness, especially when accompanied by headache, encephalopathy, or seizures. Women with suspected venous sinus thrombosis should undergo MRI and MRV of the brain. Venous sinus thrombosis is discussed further in Chap. 19.

Peripheral nerve and plexus lesions usually resolve on their own and should be managed with the expectation that they will improve. Patients with atypical examination findings may require imaging studies of the pelvis, lumbosacral spine, or brain. If symptoms do not improve by 3 weeks postpartum, nerve conduction studies and electromyography aid in lesion localization and prognosis.

Hemiparesis and Hemiplegia

Hemiparesis is due almost exclusively to dysfunction of the central nervous system. Common causes include ischemic stroke, hemorrhage, tumor, demyelination, or abscess. In exceptional cases, multiple simultaneous peripheral nervous system lesions may produce multifocal problems that masquerade as hemiparesis. The following five rules help to pinpoint the site of pathology in hemiparesis:

1. Cerebral cortical lesions producing simultaneous weakness of the face, arm, and leg should always be accompanied by some behavioral manifestation. It would be unusual for a right-handed patient with a left cortical lesion, for example, to have severe right hemiparesis without aphasia.
2. Dense subcortical lesions that involve the internal capsule produce severe hemiparesis that is usually unassociated with behavioral deficits. The most common internal capsule lesion is infarction in the territory of the medial lenticulostriate arteries (Chap. 21).
3. A brainstem lesion often produces a "crossed hemiparesis" in which the fascicles of a cranial nerve are compromised as they course ventrally through the corticospinal tract:
   (a) A midbrain lesion produces ipsilateral third nerve palsy and contralateral hemiparesis (Chap. 6).
   (b) A pontine lesion produces ipsilateral sixth and/or seventh nerve palsy and contralateral hemiparesis (Chaps. 6 and 8).
   (c) A medullary lesion produces ipsilateral 12th nerve palsy and contralateral hemiparesis (Chap. 8).
4. Small lacunar infarcts of the contralateral corona radiata, internal capsule, or pons may lead to a pure motor syndrome or ataxic hemiparesis (Chap. 21) in which the contralateral limb is both clumsy and weak.
5. Hemiparesis which spares the face is generally the result of an ipsilateral cervical spinal cord lesion (Chap. 17) but may also occur with cerebral lesions.

Multifocal Weakness

Multifocal weakness is always due to multifocal nervous system disease. The common localizations of multifocal weakness are the central nervous system white matter, anterior horn cells, nerve roots, and peripheral nerves. Common conditions that produce multifocal weakness include multiple sclerosis (Chap. 22), motor neuron disease (Chap. 10), and cervical and lumbosacral radiculopathy (Chap. 17). In some cases, multiple simultaneous embolic strokes or hemorrhages may lead to multifocal weakness. The following are three important but uncommon disorders of the peripheral nervous system which produce multifocal weakness:

Vasculitic Mononeuropathy Multiplex

Mononeuropathy (mononeuritis) multiplex is an uncommon diagnosis, usually associated with vasculitis. Although referrals of patients with vague pain syndromes for mononeuropathy multiplex evaluation are common, true mononeuropathy multiplex is not subtle, and patients often have profound multifocal weakness. In many cases, the first mononeuropathy of mononeuropathy multiplex resembles a stroke in tempo and severity. The most common affected nerves are the sciatic, peroneal, radial, and ulnar. The site of nerve involvement is classically at the vascular watershed territories in the middle of the femur or humerus, but any segment of the nerve may be affected. Attacks of mononeuropathy multiplex are typically painful and result in flaccid weakness. A generalized polyneuropathy is often identified in the background (Chap. 15). The diagnosis of vasculitic mononeuropathy multiplex is established by finding lymphocytic infiltration of blood vessels with fibrinoid necrosis, though the sensitivity of nerve biopsy is modest [5]. Among the most common causes of mononeuropathy multiplex are polyarteritis nodosa, Wegener granulomatosis, cryoglobulinemic vasculitis, and rheumatoid arthritis. Diagnostic studies should include measurement of erythrocyte sedimentation rate, ANCA, cryoglobulins, hepatitis serologies, and rheumatoid factor. Evaluation should always be conducted in conjunction with a rheumatologist. The mainstay of treatment of vasculitic neuropathy is high-dose oral steroids, usually prednisone starting at a dose of 60 mg qd. Patients with rapidly progressive or new symptoms despite steroids should be treated simultaneously with cyclophosphamide or rituximab. Chronic maintenance with azathioprine or mycophenolate mofetil is often necessary. Recovery is typically very slow and incomplete. Patients must be counseled that the purpose of immunosuppression is to prevent new attacks and that it does not accelerate recovery from previous or ongoing ones.

Multifocal Motor Neuropathy with Conduction Block (MMNCB)

Patients with MMNCB are typically younger or middle-aged men who develop focal arm weakness in the distribution of a named nerve [6]. Because the weakness

begins so suddenly and is usually not associated with pain, patients are often evaluated for stroke. As the disease progresses, additional motor nerves become involved, and at this stage, MMNCB may resemble motor neuron disease. Nerve conduction studies confirm the presence of conduction block. Approximately 50% of patients with MMNCB will have antibodies to the ganglioside GM_1. Intravenous immunoglobulin is the most effective treatment for MMNCB.

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP)

HNPP is an autosomal dominantly inherited neuropathy characterized, as its name suggests, by the development of multiple pressure palsies. Carpal tunnel syndrome, ulnar neuropathy, and peroneal neuropathy recur at different times over many years. The diagnosis is established by finding a deletion of the PMP22 gene. The mainstay of treating HNPP is counseling the patient to avoid the activities that precipitate pressure palsies.

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Rapidly Progressive Weakness

12

Neuromuscular Respiratory Failure

The priority in evaluating the patient with rapidly progressive weakness is to determine whether they will require immediate intubation. Warning signs of impending respiratory disaster include tachypnea, punctuated speech, and accessory respiratory muscle use. Check inspiratory muscle strength at the bedside by asking the patient to count to 30 as quickly as possible. The ability to do so in a single breath suggests sufficient diaphragmatic strength to maintain adequate gas exchange. While performing the initial bedside assessment, check for a strong, forceful cough which indicates the ability to clear the airway.

Unlike most cardiopulmonary sources of respiratory distress, early neuromuscular respiratory failure is usually not accompanied by a decline in oxygen saturation. Similarly, typical arterial blood gas abnormalities that reflect hypoventilation (low P_{O2} and high P_{CO2}) do not appear early enough to predict the need for intubation. Rather, bedside spirometry is the most important quantitative measurement of neuromuscular respiratory failure. The two most important spirometry parameters are the negative inspiratory force (NIF) and forced vital capacity (FVC). Values which should prompt you to consider intubation or at least monitoring in an ICU setting are an NIF less than 40 cm H_20 and an FVC less than 1 liter. Use clinical judgment in interpreting these numbers, as poor patient effort and bulbar weakness (resulting in inability to form an adequate seal around the spirometer) lead to false-positive results.

The Initial Pattern of Weakness

All severe generalized weakness ultimately produces a flaccid, intubated patient. It is the initial pattern of weakness, therefore, that helps to determine its localization and possibly its etiology. Severe weakness beginning in the extraocular muscles and descending over hours suggests botulism. Fluctuating extraocular weakness with

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ptosis for several days or more prior to the onset of generalized weakness is most consistent with myasthenia gravis. Weakness that begins in the bulbar muscles, descends rapidly, and is accompanied by a pharyngeal exudate is classic for diphtheria. Limb weakness sparing the face is most consistent with cervical spine pathology. Weakness that begins in the legs and ascends rapidly over several days to a few weeks is the classic (but not exclusive) presentation of Guillain-Barre syndrome. Generalized weakness that develops over seconds is most consistent with ischemia or hemorrhage in the ventral pons.

Neurologic Examination

Though many patients with rapidly progressive weakness are intubated and incapable of cooperating with the neurologic examination, it is essential to perform as thorough an assessment as the circumstances will allow. Mental status should be tested in as much detail as possible in order to exclude coma and severe encephalopathy masquerading as weakness (see Chaps. 1 and 2). Important components of cranial nerve examination include pupillary reactions and eye movements. Approximately half of patients with botulism will have absent pupillary reactions [1]. While diplopia and ptosis are common to many causes of rapidly progressive weakness, fluctuating rather than fixed extraocular muscle weakness strongly suggest myasthenia gravis. Preserved vertical eye movements in a tetraplegic, seemingly unresponsive patient point to a locked-in state caused by pontine hemorrhage or infarction. Deep tendon reflex testing is very important in patients with rapidly progressive weakness: hyporeflexia or areflexia are prerequisites for the diagnosis of Guillain-Barre syndrome. While spasticity and hyperreflexia might be expected in central nervous system disorders, patients with spinal cord lesions severe enough to produce spinal shock are flaccid and areflexic initially. Sensory examination is often unhelpful in patients with rapidly progressive weakness, as cooperation is usually limited. In a patient who is sufficiently awake, decreased sensation points to a peripheral nerve or spinal cord lesion, whereas preserved sensation makes the muscle or neuromuscular junction more likely localizations.

Diagnostic Studies

If there are signs of a specific etiology of rapidly progressive weakness, investigations should be tailored to confirm that diagnosis. In many cases, however, a broad spectrum of studies is required, as the diagnosis is not apparent from the clinical history and examination. Although this “shotgun” approach may appear inelegant, the gravity of rapidly progressive weakness and limitations in the examination necessitate a thorough battery of tests. The most important diagnostic tools are neuroimaging studies of the brain and spine, nerve conduction studies (NCS) and electromyography (EMG), and lumbar puncture.

Neuroimaging Studies

In most cases, rapidly progressive weakness results from injury to the peripheral rather than to the central nervous system. In some cases, however, ischemic, inflammatory, or space-occupying lesions of the central nervous system may produce acute-onset weakness. MRI of the brain and entire spine with and without contrast should be performed if central nervous system injury is suspected or if evaluation of the peripheral nervous system is unrevealing.

Electromyography (EMG) and Nerve Conduction Studies (NCS)

EMG and NCS are the most useful diagnostic studies for localizing the source of rapidly progressive weakness. NCS involve stimulating and recording from a select group of sensory and motor nerves with measurement of amplitude and velocity of peripheral nerve responses. Needle EMG allows recording of spontaneous activity from muscles and motor unit analysis and is helpful in patients with muscle, nerve, and nerve root disease. Repetitive nerve stimulation and single-fiber EMG are special studies which assess the neuromuscular junction.

Neurophysiologic testing has several important limitations when used for evaluation of patients with severe generalized weakness. First, a fair amount of cooperation is required for needle EMG, and single-fiber EMG is essentially impossible in severely encephalopathic patients. Second, many patients with severe weakness are intubated and have a variety of intravenous lines and other catheters that prevent adequate skin exposure for electrode placement. Finally, electrical interference from intensive care unit equipment creates excessive electrical noise that makes signal interpretation challenging.

The following is a brief summary of the most important patterns of EMG and NCS abnormalities in patients with rapidly progressive weakness:

Demyelinating Neuropathy

The neurophysiologic hallmark of Guillain-Barre syndrome is acquired demyelination: NCS show prolonged distal latencies, markedly slowed conduction velocities (less than 75% of normal values), abnormal temporal dispersion, conduction block, and prolonged late responses (see Chap. 10, Fig. 10.4). Many of the findings of primary demyelination are not present in early Guillain-Barre syndrome: prolonged or absent H and F responses may be the only nerve conduction abnormalities in early disease [2]. Severe Guillain-Barre syndrome is accompanied by decreased motor response amplitudes that reflect axonal loss. Needle EMG showing decreased motor unit recruitment may be the only electrophysiologic abnormality in the first week of the disease. As Guillain-Barre syndrome progresses, signs of denervation including fibrillation potentials and positive sharp waves develop.

Axonal Neuropathy

Axonal neuropathies are less likely to lead to rapidly progressive weakness than are demyelinating ones. Neurophysiologic characteristics of axonal neuropathy include low response amplitudes and mildly reduced (never below 75% of normal) conduction velocities. EMG shows decreased motor unit recruitment and fibrillation potentials. Axon loss may be seen with severe Guillain-Barre syndrome, but findings of axon loss should prompt investigation for heavy metal intoxication, porphyria, and vasculitis.

Presynaptic Neuromuscular Junction Dysfunction

Botulism is the most important presynaptic neuromuscular junction disorder leading to rapidly progressive weakness. The hallmark of presynaptic neuromuscular junction dysfunction is that exercise or fast repetitive nerve stimulation results in an increase in motor amplitudes (see Chap. 10, Fig. 10.3).

Postsynaptic Neuromuscular Junction Dysfunction

Myasthenia gravis and other postsynaptic neuromuscular junction transmission disorders are accompanied by abnormal decremental responses with repetitive nerve stimulation (Chap. 10, Fig. 10.2). If it is technically possible in the ICU, perform single-fiber EMG to investigate for increased jitter and blocking.

Myopathy

Muscle diseases are uncommon causes of rapidly progressive weakness but may prevent a patient from being weaned from the ventilator. The electromyographic characteristics of myopathy are short duration, small amplitude, and polyphasic motor units with early recruitment. Motor nerve conduction studies may show decreased response amplitudes, while sensory nerve conduction studies are normal.

Cerebrospinal Fluid (CSF) Analysis

The characteristic CSF finding in Guillain-Barre syndrome is albuminocytologic dissociation in which elevated protein is accompanied by a normal white blood cell count. This abnormality, however, is present in only 70% of patients within 1 week of symptom onset [2]. The spinal fluid in acute disseminated encephalomyelitis and other inflammatory myelopathies shows increased white blood cell counts and protein. Viral antibodies are present in patients with poliomyelitis due to West Nile virus.

Blood, Urine, and Stool Examination

Abnormalities in the blood, urine, and stool may be diagnostic in some patients with rapidly progressive weakness. Patients with lead, arsenic, or thallium poisoning will have elevated levels of the relevant heavy metal. Antibodies to West Nile virus are seen in some patients with poliomyelitis. Antibodies to the acetylcholine receptor or muscle-specific tyrosine kinase are present in most patients with myasthenic crisis. If tested early enough in the course, botulinum toxin is detectable in the stool or serum of patients with botulism [1]. Elevated levels of 24-hour urine porphobilinogen excretion are diagnostic of porphyria.

Common Causes of Acute Paralysis

Guillain-Barre Syndrome (GBS)

Guillain-Barre syndrome (GBS) or acute inflammatory demyelinating polyradiculoneuropathy (AIDP) is the most common source of acute-onset generalized paralysis in the United States. As its name suggests, it is an autoimmune demyelinating disorder of the peripheral nerves and nerve roots. The classical clinical history begins with a prodrome of gastrointestinal or respiratory illness or vaccination, followed several weeks later by numbness and tingling in the extremities and weakness which begins in the feet and spreads upwards to the legs, arms, face, and respiratory muscles. Many cases of GBS, however, do not conform to this pattern, and weakness may also begin in the proximal muscles or even occasionally in the bulbar muscles. Back pain is often exquisite and may lead to exhaustive but fruitless investigation for structural spinal disease. GBS symptoms become maximal within 2–4 weeks of onset. Untreated, most patients weaken progressively, and many develop severe flaccid weakness which may progress to intubation. Occasional patients may develop only mild distal weakness and paresthesias.

The two most important physical examination findings in GBS are symmetric weakness and decreased reflexes. While there may be some side-to-side asymmetry in the early stages, the left and right sides should be symmetrically weak as the disorder progresses. Hyporeflexia and areflexia are also essential clinical features, and other diagnoses should be considered in their absence. Depending on the stage at presentation, bulbar weakness may or may not be present. Sensory loss is less severe than motor dysfunction, and large fiber modalities such as vibration and proprioception are more affected than small-fiber modalities such as pinprick and temperature.

In many cases, the diagnosis of GBS is obvious from the clinical history and examination. Lumbar puncture and EMG play a confirmatory role but may be especially important in patients with very early disease in whom the syndrome is incomplete. Albuminocytologic dissociation of the cerebrospinal fluid is defined as a high protein and low white blood cell count (<10 cells/mm^3) and is present in approximately 70% of patients with symptom duration of 1 week or less [2]. If more than 10 cells/mm^3 are present, consider alternate explanations such as HIV seroconversion or lymphoma [3]. EMG findings diagnostic of GBS (discussed above) are present in only 50% of patients within the first 5 days of symptoms [2].

Intravenous immunoglobulin (IVIg) and plasmapheresis are the mainstays of immunomodulatory therapy in GBS. IVIg is administered at a dose of 2 g/kg, usually divided over 5 days. Important side effects of IVIg include headache, flulike symptoms, aseptic meningitis, kidney failure, and hypercoagulability. Plasmapheresis is performed as a series of five exchanges every other day. Complications of plasmapheresis include those related to central line insertion, fluctuations in blood pressure due to large-volume fluid shifts, hypocalcemia, and removal of clotting factors which can lead to bleeding. Both IVIg and plasmapheresis reduce the time required to regain the ability the walk and should be started as

quickly as possible [4, 5]. Although neither treatment is superior to the other, I choose IVIg more often, as it can be started more quickly, has fewer serious associated side effects, and in at least one high-quality study led to faster improvement than plasmapheresis [6].

Supportive care is also important in patients with GBS. Patients with airway compromise, cardiac arrhythmias, and blood pressure fluctuations should be treated in the ICU. GBS often causes severe pain which requires narcotics (including patient-controlled anesthesia in some cases) and agents for neuropathic pain.

As might be guessed, the ultimate prognosis of GBS is correlated with the maximal severity of clinical deficits. Electrophysiologically, finding reduced compound muscle action potential (CMAP) amplitudes on nerve conduction studies predicts slower and incomplete recovery. Some patients who are diagnosed and treated at an early enough stage may be able to walk out of the hospital unassisted. Recovery for patients with severe disease, however, usually takes 3–6 months or longer. Because improvement may be slow, there is often a temptation to repeat treatment with IVIg or plasmapheresis or to switch between these treatments. There is no evidence, however, to support either of these approaches. Waiting for a response to the initial therapy is likely the most appropriate action.

Myasthenic Crisis

A myasthenic crisis characterized by respiratory muscle paralysis may occur at any stage of the disorder, even as its initial presentation. It may be differentiated from the other causes of rapid onset weakness by the initial involvement of extraocular and bulbar muscles. Precipitants of myasthenic crisis include infection and medications which are known to exacerbate myasthenia gravis, especially aminoglycosides. High-dose corticosteroids prescribed for myasthenia gravis are another source of myasthenic crisis, as they may paradoxically worsen symptoms within 1 or 2 weeks of initiation. The mechanism for this worsening is unclear, but slow upwards titration of corticosteroids reduces the incidence of this phenomenon.

Myasthenic crisis should be differentiated from cholinergic crisis, a much less common disorder caused by excessive doses of acetylcholinesterase inhibitors. Telltale signs of cholinergic crisis include copious oral and nasal secretions, fasciculations, and gastrointestinal cramps. Unlike myasthenic crisis, cholinergic crisis resolves within several hours of stopping acetylcholinesterase inhibitors. In most cases, though, excessive acetylcholinesterase inhibitor use reflects undertreated myasthenia gravis and requires addition therapy to address the myasthenia.

The evaluation and treatment of suspected myasthenic crisis should start with pulmonary function testing and intubation as necessary. Superimposed respiratory, gastrointestinal, and urinary tract infections must be addressed. In rare cases, treating such an infection may resolve the crisis. Almost all patients, however, will require a series of five plasma exchanges or intravenous immunoglobulin given at a dose of 2 mg/kg divided over 5 days. Response is typically noted within 1–3 weeks. I prefer to treat myasthenics in crisis with plasmapheresis based a trend towards

more rapid improvement compared to IVIg, though meta-analyses have not shown a difference between the two treatments [7] (Gajdos et al. 1997). Patients with MuSK myasthenia gravis, in particular, are more likely to respond to plasmapheresis than to IVIg [8]. Larger doses of acetylcholinesterase inhibitors are often employed but are not helpful.

Because the benefits of plasmapheresis and IVIg are transient, disease-modifying regimens need to be augmented in patients with myasthenic crisis. Increase steroids to their goal doses while patients receive plasmapheresis or IVIg. In patients who are already taking steroids, start a steroid-sparing agent such as mycophenolate mofetil (500 mg bid to start, increase to 1000 mg bid in 1 week) or azathioprine (50 mg qd to start, increase by 50 mg per dose each week to a goal of 1–2 mg/kg). Rituximab infusions should be coordinated for patients with MuSK myasthenia. Be aware, however, that any disease-modifying agents will not provide symptomatic benefit for several months.

Brainstem Catastrophe

Large brainstem lesions, typically in the ventral pons may produce severe, instantaneous weakness. The classic example is the locked-in state caused by basilar artery thrombosis or pontine hemorrhage. This state is characterized by complete paralysis of the face and limbs with sparing of vertical eye movements and blinking. Other causes of brainstem catastrophe include inflammation, expanding neoplasm, infectious mass lesions, and central pontine myelinolysis caused by overly rapid correction of hyponatremia. Patients with suspected brainstem catastrophe should undergo MRI with diffusion-weighted imaging and contrast, and treatment should be directed at the underlying cause.

Less Common Causes of Acute Paralysis

Botulism

Foodborne botulism is an uncommon form of acute-onset paralysis caused by ingestion of botulinum toxin, an inhibitor of presynaptic acetylcholine release [1]. Gastrointestinal distress usually begins 12–36 hours after toxin ingestion. Diplopia, ptosis, dysarthria, and dysphagia are the first neurologic symptoms. Large unreactive pupils are present in approximately 50% of patients with botulism, distinguishing the disorder from other causes of acute paralysis. Weakness of the arms, respiratory muscles, and legs follows within several hours to a few days. The toxin may be identified from the serum or stool if checked within 48–72 hours of symptom onset. Nerve conduction study findings of botulism include small motor amplitudes which increase in size with sustained exercise or rapid (50 Hz) repetitive nerve stimulation. If botulism is strongly suspected, then initiate treatment with heptavalent antitoxin, available from the Centers for Disease Control. Although this intervention will not reverse active symptoms, it may prevent new ones from

developing. Recovery from foodborne botulism usually takes many months, but the prognosis is good if the comorbidities of chronic ventilation can be avoided.

Wound botulism and hidden botulism are less common than foodborne botulism. Wound botulism was described initially in patients with deep traumatic injuries, but it is now most common in users of black tar heroin in California and other parts of the Western United States [9]. The clinical presentation is similar to foodborne botulism, though patients may not have gastrointestinal symptoms. Patients should be treated with wound debridement, antibiotics, and antitoxin. Hidden botulism is the adult analog of infant botulism: a patient with a gut uncolonized by protective bacteria (often in the perioperative setting) develops botulism due to ingestion of the organism and elaboration of spores within the gut [10]. Patients with hidden botulism should be treated with antitoxin.

Uncommon Polyneuropathies

Several uncommon polyneuropathies may produce an acute paralysis that mimics Guillain-Barre syndrome (GBS). Because these neuropathies are all rare, they will be mentioned only briefly (Table 12.1).

Poliomyelitis

Widespread vaccination has made poliomyelitis due to poliovirus uncommon in the United States, but it still affects patients in the developing world. After a viral prodrome, patients develop painful monoparesis followed by the rapid onset of flaccid

Table 12.1 Uncommon neuropathies which cause rapidly progressive weakness

Condition	Clinical clues	Diagnostic test	Treatment
Arsenic	Mees' lines (white lines on the fingernails)	Elevated serum arsenic levels	Dimercaprol or dimercaptosuccinic acid
Lead	Abdominal pain, anemia	Elevated serum lead levels	Dimercaprol and EDTA
Thallium	Alopecia	Elevated serum thallium levels	Prussian blue
Porphyria	Abdominal pain, psychiatric disturbance	Elevated 24-hour urine porphobilinogen	Hematin and glucose
Peripheral nerve vasculitis (polyarteritis nodosa, Churg-Strauss, rheumatoid arthritis)	Rash, involvement of other organ systems	Elevated ESR, rheumatoid factor, positive hepatitis serologies, eosinophilia, abnormal ANCA Consider rheumatology consultation	Prednisone +/− cyclophosphamide or rituximab
Diphtheria	Pharyngeal exudate	Culture of pharyngeal membrane	Antitoxin plus penicillin
Beriberi	Malnutrition, alcoholism, gastric bypass	Decreased thiamine level	Thiamine supplementation

paralysis. During the acute phase, the spinal fluid of patients with poliomyelitis shows an increased neutrophil count which distinguishes it from Guillain-Barre syndrome. West Nile virus is a more common cause of poliomyelitis in the United States and may be diagnosed by finding antibodies in the serum or spinal fluid [11].

Spinal Cord Insults

Lesions of the high cervical spinal cord may produce acute paralysis of all four limbs while sparing the face. Important spinal processes that cause rapidly progressive weakness include trauma, herniated intervertebral discs, transverse myelitis, and spinal cord stroke (Chaps. 17 and 22).

Difficulty Weaning from the Ventilator

Difficulty weaning from the ventilator is usually due to cardiopulmonary disease [12]. In some cases, intensivists are not able to find a cardiopulmonary source for failure to wean, and neurologists are consulted. Begin the diagnostic process by addressing possible central nervous system processes such as coma and encephalopathy. Next, exclude disorders acquired prior to intubation such as Guillain-Barre syndrome and myasthenia gravis. Finally, investigate for neuromuscular disorders acquired in the intensive care unit including critical illness polyneuropathy, critical illness myopathy, and prolonged neuromuscular junction blockade.

Critical Illness Polyneuropathy

Critical illness polyneuropathy (CIP) occurs in the setting of severe sepsis and multiorgan failure, usually in patients with intensive care unit stays of at least a week in duration [13]. Clinically, CIP is characterized by flaccid areflexic weakness and sensory loss. Nerve conduction studies show evidence for axonal polyneuropathy in the form of low sensory and motor response amplitudes. EMG shows fibrillations and positive sharp waves reflective of denervation. Unfortunately, there is no specific treatment for CIP, and patients who have the condition usually need several months (or longer) for axonal regrowth and clinical recovery to take place. Improvement is often incomplete.

Critical Illness Myopathy

Critical illness myopathy (CIM) also occurs in the setting of severe sepsis. The use of corticosteroids and neuromuscular junction blocking agents are additional risk factors for CIM [14]. Patients with CIM are usually weak and areflexic, much like those with CIP. The sensory examination in CIM, if assessable, should be normal.

Creatine kinase levels may be normal, modestly elevated, or markedly elevated. Nerve conduction studies show decreased motor response amplitudes with normal sensory response amplitudes. Like CIP, needle EMG shows signs of denervation including fibrillation potentials and positive sharp waves. If motor units can be activated, they are small and polyphasic and show early recruitment. It is often difficult to distinguish between CIM and CIP by clinical examination and standard neurophysiologic assessment, and many patients have both conditions simultaneously. The best way to distinguish between the two is by finding electrical inexcitability upon direct muscle stimulation in CIM [15]. The distinction between CIP and CIM is not necessarily critical, as neither has a specific treatment, and both require weeks to months of supportive care before a substantial improvement occurs.

Prolonged Neuromuscular Junction Blockade

Neuromuscular junction blocking agents are used to paralyze patients for surgery or to maintain an airway in patients with cardiopulmonary disease who are resisting the ventilator. Weakness may persist for several days after these agents are withdrawn, especially in patients with hepatic or renal dysfunction [16]. Although abnormal repetitive nerve stimulation may help to diagnose prolonged neuromuscular junction blockade, interference from electrical equipment in the ICU generally makes this technique impractical. Other than discontinuing the responsible agents and waiting for recovery, there is no specific treatment for prolonged neuromuscular junction blockade. While most patients recover in a few days, some have prolonged deficits which may overlap clinically with CIM.

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Parkinsonism

13

History

Parkinsonism refers to the combination of bradykinesia (slowness of movement) and rigidity. It is the core feature of Parkinson disease and other disorders of the extrapyramidal system such as progressive supranuclear palsy, multisystem atrophy, and corticobasal degeneration. A patient with parkinsonism may describe their problem as slowness or stiffness, but they may also say that they have no energy or that they are weak. Parkinsonism is often attributed to fatigue, normal aging, or depression for months or even years, and a patient with parkinsonism may only come to neurological attention after they develop a tremor or gait impairment. The following are the important elements of the history in patients with parkinsonism:

Age of Onset

Parkinsonism is generally a problem of older patients. Symptoms beginning before age 40 suggest an early onset or familial variant of Parkinson disease, a toxin- or medication-related process, or Wilson disease.

Pace of Onset

Most forms of parkinsonism become clinically apparent over a course of months to years. Examples include Parkinson disease, multisystem atrophy, and progressive supranuclear palsy. Apoplectic symptom onset is exceptionally rare and is usually due to bilateral caudate, putaminal, or thalamic infarcts [1]. Symptoms that develop over days to weeks may be due to drug-induced parkinsonism (a condition that may also develop over several years).

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Presence of Tremor

Asymmetric resting hand (or less likely, foot) tremor strongly suggests a diagnosis of Parkinson disease. Large amplitude action or intention tremors are more typical of Wilson disease. Tremor is usually absent in atypical forms of parkinsonism – when present, it is often mild, symmetric, and occurs with action rather than with rest. Chapter 14 provides a more detailed discussion of the evaluation and treatment of tremor.

Gait Dysfunction and Falls

Almost all patients with parkinsonism eventually develop gait abnormalities, usually as a later feature of disease. Gait difficulty at or shortly after symptom onset suggests progressive supranuclear palsy or vascular parkinsonism. Common descriptions of gait abnormalities in parkinsonism include stiff leggedness, shuffling, slowness, and walking with a lack of arm movement.

Left-Right Symmetry

Parkinson disease is usually asymmetric in its early stages. As the disease advances, however, both sides become involved, and the patient eventually has symmetric deficits. With the exception of corticobasal ganglionic degeneration, most other forms of parkinsonism are relatively symmetric.

Autonomic Symptoms

Autonomic dysfunction including dry mouth, decreased perspiration during exercise, lightheadedness, fainting, constipation, and urinary retention is prominent in multisystem atrophy and usually is more impressive than either rigidity or bradykinesia. Autonomic symptoms are also common in Parkinson disease but are usually not the presenting symptoms.

Ataxia

Symptoms of ataxia including clumsiness, frequent spilling of food or liquids, and dropping things are most common in multisystem atrophy. These symptoms are more prominent than extrapyramidal ones in some patients with multiple system atrophy and the cerebellar ataxias.

Medications and Toxins

Dopamine antagonists used as antipsychotics and the promotility agent metoclopramide are the most common precipitants of drug-induced parkinsonism. Drugs of

abuse are sometimes adulterated with substances that precipitate parkinsonism. Other uncommon toxins that may produce parkinsonism include manganese and carbon monoxide.

Family History

Familial forms of Parkinson disease may be due to genetic disorders, inherited in both autosomal dominant and recessive fashions [2]. Huntington disease (autosomal dominant) and Wilson disease (autosomal recessive) are among the more common inherited forms of parkinsonism. In most patients, however, the family history is noncontributory.

Dementia

Memory loss and behavioral changes affect approximately 25–30% of patients with Parkinson disease but are not prominent in early disease [3]. Dementia with Lewy bodies, Huntington disease, progressive supranuclear palsy, and corticobasal degeneration are causes of parkinsonism with dementia as an early or initial feature, often as the major symptom.

Activities of Daily Living

It is often helpful to ask the patient if it takes them more time to get ready in the morning, whether it is more difficult to turn over or get out of bed, and whether they have difficulty with eating. Impaired activities of daily living, while not necessarily helpful in differentiating among the various forms of parkinsonism, aid in the determination of disease severity and guides treatment initiation.

Examination

Rigidity

Rigidity is an increase in tone that is independent of the velocity, displacement, and direction of movement. It is the form of hypertonicity produced by extrapyramidal disease. Rigidity may affect the appendicular or axial musculature. Evaluate for appendicular rigidity at the elbow, wrist, knee, and ankle. When testing for rigidity, look for an increase in tone in response to distraction: ask the patient to rapidly tap the opposite hand or foot, trace broad circles in the air, or recite the months of the year backwards. These maneuvers may uncover rigidity that was not apparent at rest. Test for axial rigidity by examining tone in the neck and torso. With the patient sitting up straight but relaxed in a chair, grasp their head firmly by the sides and attempt to move it briskly in the anterior-posterior plane. Normally, the neck is quite loose, and there will be little resistance to this movement. In a patient with axial

rigidity, however, the whole trunk will move in unison with the head. Cogwheel rigidity occurs when a tremor is superimposed on a background of rigidity. This is most easily elicited by rotating the hand at the wrist and feeling for a ratchety resistance.

Bradykinesia

Bradykinesia, or slowness of movement, is often overlooked by non-neurologists or dismissed as a manifestation of normal aging. Masking of facial expression, reduced blinking frequency, and slowness of speech and gait are all signs of bradykinesia that may be observed without formal testing. Look for bradykinesia on examination by asking the patient to rapidly tap their fingers together, alternately slap the palmar and dorsal surfaces of the hand against their thigh, and elevate the leg slightly and tap the ground with the front of the foot. Observe for slowness, decomposition, or inability to perform these movements. A decrement of both amplitude and velocity with hand or foot tapping is most consistent with bradykinesia.

Tremor

Asymmetric resting tremor is one of the findings that most reliably distinguishes between Parkinson disease and other forms of parkinsonism. Chapter 14 contains a detailed discussion of the tremor of Parkinson disease and other movement disorders.

Gait

The typical features of an extrapyramidal gait are a relatively narrow base, slow initiation, shortened stride length, and slow turns. A patient with Parkinson disease is characteristically hunched over at the shoulders, whereas a patient with progressive supranuclear palsy tends to be hyperextended throughout the trunk. The cerebellar form of MSA may be associated with an ataxic gait. Chapter 18 contains a more detailed discussion of the gait abnormalities of patients with extrapyramidal disease.

Speech

Dysarthria is discussed in further detail in Chap. 8. It may be a useful sign in differentiating among the various forms of parkinsonism. Early spastic dysarthria suggests atypical parkinsonism, especially progressive supranuclear palsy. A high-pitched quivering dysarthria accompanies multisystem atrophy but usually develops in the later stage of the disease. Hypophonia and bradykinesia are the most common speech abnormalities in Parkinson disease.

Mental Status Examination

Perform a complete mental status examination (Chap. 4) in all patients with parkinsonism, as cognitive abnormalities are common in patients with extrapyramidal disease, and specific abnormalities may help to differentiate among the various disorders. Dementia in parkinsonism is usually dominated by cognitive slowing rather than by the frank memory deficits that characterize Alzheimer disease. Problems with processing speed and visuospatial abnormalities are the most common findings on mental status examination. Asymmetric limb apraxia is particularly suggestive of corticobasal degeneration and may be the presenting feature in some patients. The cognitive features of dementia with Lewy bodies are discussed further in Chap. 4.

Eye Movements

Examining saccadic eye movements is essential in patients with suspected progressive supranuclear palsy. To test saccades, instruct the patient to first look at your nose. Next, ask them to quickly shift their gaze up, down, to the left, and to the right. Poor initiation, decreased velocity, and decreased amplitude of downward saccades are classical features of progressive supranuclear palsy but may be absent early in the course of the disease. If downward saccades are absent, attempt to prove that the saccadic disorder results from supranuclear dysfunction by looking for a preserved oculocephalic reflex: quickly thrust the head backwards and observe for an intact downward vestibulo-ocular response.

Orthostatic Hypotension

Autonomic dysfunction is the main problem in many patients with multisystem atrophy and may also be a disabling component of Parkinson disease. Testing for orthostatic hypotension is described in further detail in Chap. 9.

Laboratory and Neuroimaging Studies

Brain MRI

In most cases, neuroimaging is of limited utility in evaluating parkinsonism. Brain MRI is mainly employed to exclude the possibilities of vascular parkinsonism, tumors, and hydrocephalus. Patients with rapid-onset disease should undergo diffusion-weighted imaging to look for ischemic lesions or evidence of Creutzfeldt-Jakob disease. In some cases, MRI may help to distinguish among the different forms of parkinsonism. Brain MRI of a patient with multisystem atrophy may show atrophy of the pons and cerebellum and the hot cross bun sign (crossed T2

hyperintensities) in the pons (Fig. 13.1). Progressive supranuclear palsy leads to atrophy of the midbrain giving it a "hummingbird" appearance (Fig. 13.2). Huntington disease leads to prominent atrophy of the caudate nuclei (Chap. 14, Fig. 13.1).

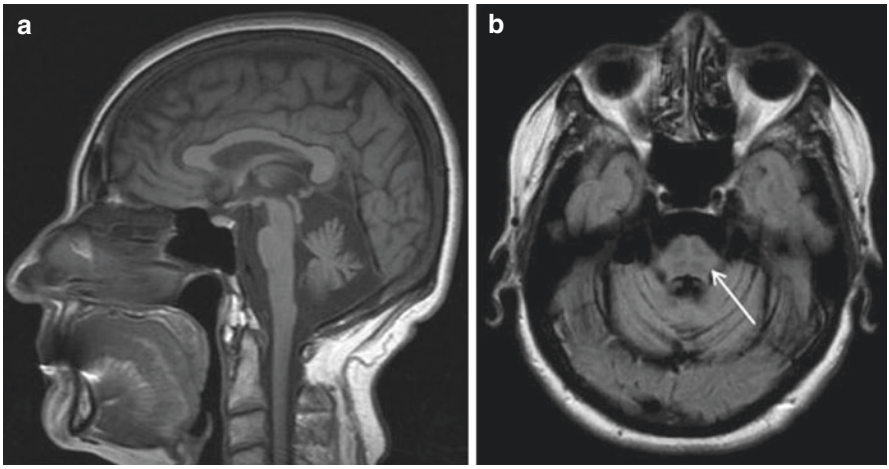

Fig. 13.1 In general, neuroimaging studies are not particularly helpful in the diagnosis of parkinsonism. In this patient with multisystem atrophy, however, brain MRI shows (**a**) atrophy of the pons and cerebellum on sagittal view and (**b**) the pathognomonic "hot cross bun" sign in the pons on axial view

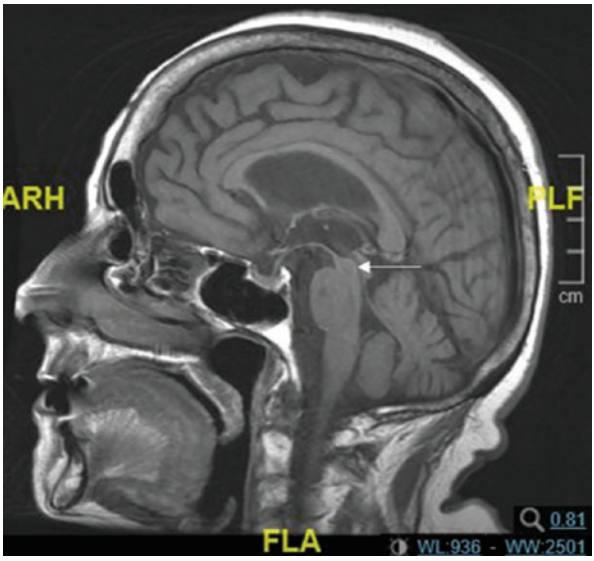

Fig. 13.2 Sagittal brain MRI demonstrating midbrain atrophy (the "hummingbird sign") in a patient with progressive supranuclear palsy

Other Studies

In younger patients, check for reduced serum ceruloplasmin levels and increased 24-hour urinary copper excretion diagnostic of Wilson disease (Chap. 14). Multigene panels are available to evaluate younger patients with presumed genetic forms of Parkinson disease. Autonomic testing to document orthostatic hypotension and other autonomic abnormalities may be valuable in the diagnosis of multisystem atrophy. Anal sphincter electromyography is often performed to distinguish MSA from PD, but it is generally less helpful than history and autonomic testing. Dopamine transporter scan demonstrating a striatal dopamine deficiency can be a useful adjunct for diagnosis of PD but does not distinguish among the various forms of parkinsonism. It is not more useful than clinical assessment and is most helpful in confirming a diagnosis of PD in patients with coexisting essential tremor [4].

Parkinson Disease

Idiopathic Parkinson disease (PD) is the most common form of parkinsonism. Patients usually develop the disorder between their 50s and 70s, although symptoms will begin before age 40 in 5–10% [5]. The cardinal features of PD are tremor, rigidity, and bradykinesia. Unfortunately, there is no laboratory test or neuroimaging study that definitively confirms PD, and the diagnosis must be made clinically. The features that most reliably distinguish PD from other forms of parkinsonism are asymmetric resting tremor and symptomatic improvement with levodopa [6]. Up to 30% of patients, however, will lack a tremor [6]. If the diagnosis is unclear, a trial of levodopa may be warranted. The presence, tempo, and relative severity of nonmotor symptoms (see below) may also help to distinguish patients with idiopathic PD from those with other forms of parkinsonism.

PD may be divided into three stages: an early, levodopa-responsive stage in which disability is minimal, an intermediate stage in which responsiveness to levodopa decreases and disability becomes more prominent, and an end-stage in which benefits from levodopa are minimal and disability becomes severe.

Treatment of Early-Stage PD

Treatment is not required for some patients with early PD who are not particularly bothered by their symptoms, as the available medications treat only the symptoms and do not change the disease course. It is acceptable to wait and pursue a course of exercise and lifestyle optimization before using any medications if the patient prefers a conservative approach.

Tremor is often the most prominent symptom in the early stages of PD, and some patients may have a milder, tremor-predominant form of the disease for many years.

The anticholinergic agent trihexyphenidyl (started at 1 mg qd and titrated up to 2–3 mg tid as needed) is the preferred treatment for a patient with isolated or predominant tremor. Side effects of this medication include sedation and dry mouth. Amantadine 100 mg bid may also be helpful for PD patients with isolated tremor. Levodopa tends to be less helpful for tremor than it is for rigidity and bradykinesia.

The treatment options for a patient with symptomatic bradykinesia or rigidity are levodopa, dopamine agonists, and monoamine oxidase B (MAO-B) inhibitors.

I use levodopa as the first medication for most patients with at least moderate disability at presentation. Side effects of levodopa include nausea, vomiting, and orthostasis and may be avoided by using levodopa in combination with the dopamine-decarboxylase inhibitor carbidopa. Carbidopa/levodopa combinations comes in 10 mg/100 mg, 25 mg/100 mg, and 25 mg/250 mg doses. I usually initiate treatment with one 25 mg/100 mg pill three times a day. Most patients who will respond to levodopa will do so at daily doses of 300–600 mg.

Dopamine agonists are options for younger patients with mild disability. The two most common agents are ropinirole (starting dose 0.25 mg tid, usual effective dose 1–3 mg tid) and pramipexole (starting dose 0.125 mg tid, usual effective dose 0.5 mg tid). Side effects of these agents include nausea, vomiting, and hypotension. Excessive daytime sleepiness, sleep attacks, hallucinations, and compulsive habits such as gambling and shopping are important but uncommon side effects of dopamine agonists. The dopamine agonist withdrawal syndrome occurs in patients in whom a dopamine agonist is removed or withdrawn and includes symptoms such as anxiety, panic attacks, depression, agitation, drug cravings, and autonomic symptoms [7]. Most patients with dopamine agonist withdrawal syndrome improve upon restarting the dopamine agonist.

The MAO-B inhibitors rasagiline (1 mg qd) and selegiline (5 mg bid) are the third main option for treating early PD. In addition to symptomatic improvement, these agents may provide neuroprotective benefits, though this is an area of great controversy [8]. There are two important interactions to keep in mind when prescribing MAO-B inhibitors: when combined with a selective serotonin reuptake inhibitor, they may lead to the serotonin syndrome consisting of confusion, autonomic instability, and myoclonus, and when combined with tyramine-rich foods such as red wine, aged cheese, or aged meat, they may precipitate a hypertensive crisis. MAO-B inhibitors may provide mild symptomatic relief for PD patients.

Treatment of Intermediate-Stage PD

Patients with PD almost inevitably progress over years. During the intermediate stage of PD, bradykinesia and rigidity worsen. Responsiveness to levodopa decreases, while side effects secondary to the medication increase. Motor fluctuations and the “wearing-off” phenomenon begin in the intermediate stage of PD: after several hours of symptomatic response to levodopa, the benefit disappears

before the next scheduled dose is administered, and the patient enters the "off state." There are several options to address the wearing-off phenomenon:

- Decreasing the interval between levodopa doses may be helpful for some patients, though doing so may worsen side effects including dyskinesias (see below).
- Combination immediate- and extended-release forms of levodopa may be substituted for the immediate-release form [9]. To do so, it is necessary to approximately double the levodopa dose in the combination form, e.g., a patient taking immediate-release carbidopa/levodopa at a dose of three tablets of 25/100 three times a day (900 mg total levodopa) will change to immediate/extended release carbidopa/levodopa at a dose of three capsules of 48.75/195 three times a day (1755 mg total levodopa).
- Add the catechol-o-methyltransferase (COMT) inhibitor entacapone (200 mg with each dose of levodopa) to extend the half-life of levodopa. The main side effect of entacapone is diarrhea. Other options to treat wearing off include adding dopamine agonists or MAO-B inhibitors.

In addition to experiencing motor fluctuations and wearing off, patients in the intermediate stage of PD also derive less benefit from each individual levodopa dose. Higher doses of levodopa, even up to a total daily dose of 1000–1200 mg, may be ineffective. It is important to determine at what times of day the patient is most symptomatic and to make sure that their levodopa is dosed adequately in anticipation of these dips. Most patients require additional medication early in the day to get through their morning routines. Others might require more levodopa at night to avoid nocturnal akinesia that prevents them from getting to the bathroom. For some patients, the problem might be eating high-protein meals that interfere with the intestinal absorption of levodopa. Address this problem by instructing the patient to take their levodopa an hour before or after meals or to eat low-protein meals in the morning. Dopamine agonists and MAO-B inhibitors may provide modest benefit for patients with diminishing responses to levodopa.

Dyskinesias secondary to levodopa use also develop in the intermediate stage of PD. Dyskinesias may affect any part of the body and are usually choreiform in nature but may take the form of any of the hyperkinetic movements (Chap. 14). Dyskinesias are generally more prominent at the time of peak levodopa effect but may also be more pronounced in the off state. In some patients, decreasing the levodopa dose reduces peak-dose dyskinesias. This intervention, though would reduce any symptomatic benefit from levodopa and increases time spent in the off state. Most patients prefer to be in the on state with dyskinesias rather than to be in the off state without dyskinesias. Amantadine (100 mg bid-tid) may provide modest benefit in reducing dyskinesias but should be used cautiously in older patients or those with cognitive dysfunction, as it may precipitate confusion.

Dystonia is another important problem encountered in the intermediate stage of PD. This is most commonly a twisting movement of the lower extremities, specifically inversion at the ankles and curling of the toes. It can occur in either the on state

or off state. Treatment of on-dystonia should include reducing the dose of levodopa if possible. Treatment of off-dystonia should include spacing levodopa doses more closely or other interventions to reduce time spent in the off state. Amantadine is often useful for reducing dystonic movements. Additional treatment options include muscle relaxants such as diazepam or baclofen or botulinum toxin injections.

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) or globus pallidus interna (GPi) are surgical options for patients with intermediate PD. DBS may improve any of the symptoms of PD, decrease the time spent in the off state, and reduce dyskinesias. Candidates for DBS must be selected carefully and evaluated by a multidisciplinary team. DBS provides at most the maximum improvement that the patient derives from medical treatment: patients with minimal or no response to levodopa are not going to improve with DBS. Unfortunately, axial symptoms including gait freezing, falls, dysarthria, and dysphagia tend to be less responsive to DBS than appendicular ones are. Older patients and patients with severe cognitive impairment are excluded as surgical candidates. Possible side effects of DBS include infection, hemorrhage, and seizure, and misplacement of the stimulator leads requiring reoperation. Stimulation-related side effects include dysarthria, weight gain, and psychiatric problems, especially depression [10]. DBS requires frequent follow-up visits for stimulator testing and programming.

Treatment of Advanced PD

In the advanced stage of PD, bradykinesia and rigidity worsen. Further increases in levodopa doses or addition of other symptomatic treatments for PD are generally unhelpful. Patients experience severe bradykinesia, termed freezing in both the "on" and "off" states. "Off freezing" occurs when patients are otherwise rigid and bradykinetic and may improve with augmentation of levodopa and dopamine agonist dosing. "On freezing" occurs during periods of relatively less bradykinesia and rigidity, with patients stopping in their tracks for a few seconds at a time; this type of freezing is more challenging to treat. Gait freezing becomes problematic in advanced PD. Falls become more frequent as postural reflexes become impaired. As a result, patients often need to use walkers or wheelchairs or become bedbound. Medical and surgical treatment of freezing gait and falls are generally ineffective. Supportive care, including treatment of nonmotor symptoms, becomes the mainstay of treatment of the advanced stage of PD.

Treatment of Nonmotor Symptoms

As PD progresses, treating nonmotor symptoms, particularly cognitive and behavioral ones, becomes increasingly important. The following are among the most important of the nonmotor symptoms of PD:

Depression

Disentangling psychomotor slowing produced by depression and bradykinesia secondary to PD is often challenging and may require formal neuropsychological or psychiatric evaluation. Depressive symptoms may affect as many as 50% of patients with PD and generally parallels the severity of cognitive impairment [11]. Selective serotonin reuptake inhibitors (SSRIs) are usually the first line of treatment but must be avoided in patients who are taking MAO-B inhibitors. Tricyclic antidepressants are also helpful, but their anticholinergic properties may worsen cognitive dysfunction. Electroconvulsive therapy is often effective for treating severe depression in PD and offers the additional benefit of mild and temporary PD symptom relief [12].

Dementia

Approximately 25–30% of patients with PD develop dementia. Executive function, processing speed, and visuospatial abilities are the cognitive domains that tend to be most severely affected. Memory and language deficits may be later occurrences. Because medications used to treat PD may contribute to cognitive deficits, a trial of decreasing or discontinuing medications may help to improve symptoms. The medications used for PD in descending order of cognitive side effect likelihood (and thus, recommended sequence of discontinuation from first to last) are:

- Anticholinergic agents
- Amantadine
- MAO-B inhibitors
- COMT inhibitors
- Dopamine agonists
- Levodopa

Acetylcholinesterase inhibitors such as donepezil or rivastigmine are somewhat effective for patients with dementia associated with PD [13].

Hallucinations and Psychosis

Hallucinations and psychosis are features of intermediate and advanced PD. They occur often as side effects of one of the medications used to treat motor symptoms, and may lead to hospitalization, or in severe cases, institutionalization. The first step in evaluating and treating these symptoms is to screen for metabolic disturbances that may cause confusion, as described in Chap. 1. Try to decrease psychoactive antiparkinsonian medications as described above. If excluding metabolic derangements and tapering medications still do not improve symptoms, consider antipsychotic agents with minimal extrapyramidal side effects such as clozapine (25–75 mg qd) or quetiapine (25 mg qd-qid). Although clozapine improves psychosis, it may cause agranulocytosis and for this reason, requires frequent white blood cell count monitoring and registration with a clozapine provider program. Pimavanserin (34 mg qd) may help patients with PD and psychosis while not worsening extrapyramidal symptoms [14].

Dysphagia

Oropharyngeal bradykinesia leads to difficulty with eating and swallowing pills and puts patients at risk for aspiration. Formal swallowing studies may help to clarify the problem if there is any doubt about the presence or severity of dysphagia. Dysphagia often responds to levodopa, provided that the patient has enough residual swallowing function to take their pills. An orally disintegrating carbidopa/levodopa formulation which dissolves on the tongue is an option. Percutaneous enteric gastrostomy tubes may be necessary for patients with severe dysphagia. For some patients with dysphagia, carbidopa/levodopa intestinal gel administered through a PEG tube with jejunal extension may help [15].

Dysarthria

Dysarthria affects up to 70% of patients with PD and usually manifests as a monotonous, hypophonic voice [16]. Although dysarthria may improve initially with levodopa, the response decreases with disease progression. Deep brain stimulation is similarly disappointing. While speech therapy (e.g., Lee Silverman Voice Therapy) may help marginally, the treatment of dysarthria related to PD is often unsatisfactory and may require assistive communication devices.

Constipation

Constipation occurs in approximately half of patients with PD and may be a disabling symptom [17]. The first step in evaluating and treating constipation is to exclude treatable medical causes. Although constipation may be related to agents used for PD including anticholinergics and levodopa, discontinuing these medications usually does not help to reverse the symptoms. Laxatives such as lactulose (30–45 mL tid-qid) and polyethylene glycol (17 g qd) are the most effective medication options. Consider referring patients with refractory symptoms to a gastroenterologist.

Atypical Parkinsonism

Progressive Supranuclear Palsy (PSP)

Although there is considerable clinical heterogeneity, PSP most commonly presents with slowness or unsteadiness of gait and falls [18]. Other presentations include dysarthria, dysphagia, and dementia. It may be difficult to differentiate PSP from other forms of parkinsonism, but the following clinical features may be helpful:

- Prominent gait instability at disease onset. Falls and other gait disturbances that occur within the first year of disease presentation are more consistent with PSP than with any of the other extrapyramidal syndromes. Patients with PSP tend to be hyperextended at the trunk, unlike those with PD who tend to be hunched over at the shoulders.

- Spastic dysarthria. Patients with PSP may have a harsh, strangled quality to their speech or may sound robotic. Amyotrophic lateral sclerosis and the pseudobulbar state affect speech in similar ways (Chap. 3).
- Supranuclear gaze palsy or slowing of vertical saccades. This is the most specific feature for PSP, but its frequent absence at disease onset often prevents definitive diagnosis. Patients with PSP have the most difficulty with looking downwards, leading to problems with reading or with spilling food while eating. Examination of saccadic eye movements is discussed above.
- Eyelid-opening apraxia. This disorder is often confused with blepharospasm, which is discussed in further detail in Chap. 6.
- Axial rigidity. Unlike PD, rigidity is greater in the axial relative to the appendicular musculature. This results in slow head turning and difficulty with truncal stability.

There is no single neuroimaging or laboratory test that confirms the diagnosis of PSP. MRI of the brain may show atrophy of the midbrain tegmentum, giving the brainstem a characteristic "hummingbird" appearance (Fig. 13.2) [19]. Ultimately, the diagnosis is established by suggestive clinical features and by exclusion of other extrapyramidal disorders. Patients in the early stages of PSP may derive mild benefit from levodopa, and a trial up to a total daily dose of 1000 mg is justifiable. As the disease progresses, supportive care becomes the mainstay of treatment. Physical therapy and occupational therapy are important for patients with PSP. Unfortunately, patients with PSP have a poor prognosis, surviving for 5–6 years, on average [18].

Multisystem Atrophy (MSA)

MSA is characterized by extrapyramidal dysfunction in combination with autonomic, cerebellar, or pyramidal dysfunction. Extrapyramidal features may be the initial and often sole manifestations of MSA for many years (MSA-P subtype), in which case it may be difficult to separate MSA from PD. Other patients present with primary autonomic dysfunction including orthostatic hypotension, hypohydrosis, and sphincter dysfunction (MSA-A subtype). Still others may have cerebellar ataxia as the predominant feature, in which case the disorder may be difficult to distinguish from an inherited spinocerebellar ataxia (MSA-C subtype). The diagnosis of MSA is usually established by clinical history and examination. Autonomic testing may help to confirm the diagnosis in patients with MSA-A. MRI of the brain demonstrating atrophy of the pons and cerebellum or the hot cross bun sign (Fig. 13.1) is most useful for patients with the MSA-C variant. Patients may respond to levodopa in the early stages of MSA, but this response declines as the disease progresses. The mainstays of treatment are symptomatic therapy for orthostatic hypotension (Chap. 9) and other autonomic nervous system problems and physical therapy and occupational therapy for the cerebellar components. Unfortunately, MSA is a progressive disabling disease, with a median survival of 6–9 years [20].

Corticobasal Ganglionic Degeneration (CBD)

CBD is an uncommon condition that is often confused with another extrapyramidal disorder such as PD or PSP or with a primary dementia [21]. Similar to PD, patients with CBD may demonstrate asymmetric rigidity and bradykinesia. Tremor, however, is usually absent. Two important findings in CBD that are unusual at presentation in other parkinsonian disorders are asymmetric limb apraxia (Chap. 4) and cortical sensory loss (Chap. 15). Limb apraxia may be accompanied by an unusual finding known as the "alien hand" phenomenon in which the affected limb seems to act of its own volition without direction from the patient. The limb apraxia may be severe to the point that it resembles a monoparesis of the affected limb and leads to trophic changes in the skin. Many patients with CBD are demented at presentation. Unlike dementia in other extrapyramidal disorders, the dementia in CBD affects cortical function such as memory and language. Dysarthria and vertical gaze impairments may lead to confusion of CBD with PSP. Patients with CBD respond minimally to levodopa, and supportive therapy is the mainstay of treatment.

Other Causes of Parkinsonism

Drug-Induced Parkinsonism

Dopamine antagonists including antipsychotics and the antiemetic metoclopramide may precipitate parkinsonism. Although symptoms tend to be relatively symmetric in drug-induced parkinsonism, a large fraction of patients with drug-induced PD will have a degree of asymmetry suggestive of idiopathic PD [22]. Only a minority, however, will have resting tremor. Removing the offending agent may lead to mild symptomatic improvement. Treatment with levodopa or with a dopamine agonist is usually not effective and should be avoided in most cases.

Vascular Parkinsonism

Parkinsonism due to cerebrovascular disease is perhaps only 5% as common as idiopathic PD but in some series represents the second most common cause of parkinsonism after PD [23]. Although patients often have a history of clinical stroke, this is not a requirement for diagnosis as many patients have parkinsonism on the basis of the cumulative effect of small, clinically silent strokes. The lower half of the body is more commonly affected, and gait disturbance is often the presenting symptom ("lower half parkinsonism"). Tremor is usually absent, and symptoms tend to be relatively symmetric. Dementia, corticospinal tract findings such as spasticity and hyperreflexia, and urinary incontinence may accompany vascular parkinsonism. Unfortunately, vascular parkinsonism does not respond to levodopa, making supportive care the mainstay of treatment.

Other Extrapyramidal Disorders

Other disorders leading to parkinsonism include those that have more prominent hyperkinetic features (Huntington disease and Wilson disease, Chap. 14) or dementia (dementia with Lewy bodies, Chap. 4) at onset.

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Hyperkinetic Movement Disorders

14

Introduction

Although classically associated with basal ganglia dysfunction, hyperkinetic movement disorders may be due to pathology at almost any level of the central nervous system, and in some cases, the peripheral nervous system. Abnormal hyperkinetic movements are usually obvious while sitting face to face with a patient and taking their history. If not, it is best to ask the patient to demonstrate the movements, as verbal descriptions are often vague or inaccurate. When examining a patient with a hyperkinetic movement disorder, it is important not only to describe and classify the movement, but also to perform a comprehensive neurologic history and examination to determine whether the abnormality is a sign of a systemic metabolic process or neurodegenerative disease.

Tremor

Tremor is the rhythmic oscillation of a body part caused by alternating contraction of agonist and antagonist muscles. Patients describe tremor as shaking or trembling, or may specifically use the word tremor. Some may even diagnose themselves (usually incorrectly) with Parkinson disease. Most tremors involve the upper extremities, and these will be discussed in greatest detail. Tremors that involve other parts of the body include essential tremor involving the head and voice, oculopalatal myoclonus, perioral and leg tremors in Parkinson disease, and leg tremor upon standing in patients with orthostatic tremor.

The first step in classifying tremor is to define it as a resting tremor, action (or postural) tremor, or intention tremor. Resting tremor is present with rest and improves or disappears with movement. Action or postural tremor develops when moving or holding a body part against gravity. Intention tremor worsens with precise, target-directed movements. In order to determine whether a patient has a

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resting, postural, or intention tremor of the upper extremity, examine them in the following five positions:

- With their hands placed palm-side down in their lap
- With their hands placed on their lap midway between pronation and supination
- With their arms pronated and outstretched in front of them
- While they move their finger rapidly back and forth between your finger and their nose
- When they attempt to reach out for a cup of water and then grasp it and bring it to their lips

The conventional elements of a tremor description include details about its frequency, amplitude, presence with rest or activity, direction, and location. As an example of this template, a typical Parkinsonian tremor would be described as "a 3–4 Hz, small-amplitude resting tremor involving flexion-extension of the left wrist."

Action Tremor

Essential Tremor

Essential or benign familial tremor is the most common type of tremor, and indeed the most common movement disorder. It typically begins in early middle age, and there is often a family history of the same tremor. The tremor is principally an intermediate frequency, small-to-medium amplitude, symmetric action tremor of the hands. Involvement of the head (including "yes-yes" or "no-no" forms) and voice is common. The feet and legs tend to be less affected. Patients may report an improvement in the tremor with alcohol ingestion and an exacerbation of the tremor with stress or anxiety.

Many patients with essential tremor have mild symptoms and do not require treatment. Primidone and propranolol are the first-line medication options and are effective in about 2/3 of patients with essential tremor. In some patients, these two medications are more effective in combination than by themselves. Other medication options are listed in Table 14.1. Deep brain stimulation of the ventral intermediate nucleus of the thalamus should be considered for patients with refractory tremor. Botulinum toxin injections may be useful for patients with vocal or head tremors.

Wilson Disease

Wilson disease is an autosomal recessive disorder of copper metabolism that produces a combination of neurologic, psychiatric, and hepatic dysfunction. Although symptoms usually develop in children and young adults, rare patients come to clinical attention in middle age or later. The neurologic symptoms in Wilson disease are variable and can include tremor, parkinsonism, dysarthria, ataxia, and dystonia. The classic but uncommon tremor in Wilson disease is a wing-beating tremor which is of high-amplitude and low frequency and is observed when the arms are

Table 14.1 Treatment options for essential tremor

Medication	Starting dose	Titration instructions	Side effects
Propranolol[a]	60 mg qd	Increase by 60 mg qd as needed to goal dose of 120–600 mg qd	Orthostatic hypotension, bradycardia, fatigue, depression
Primidone[a]	25 mg qd	Increase by 25 mg qd each week to goal of 100 mg, then increase by 50 mg qd each week to goal dose of 250–500 mg qd as needed	Sedation, ataxia
Clonazepam	0.5 mg qhs	Increase to goal dose of 1–2 mg bid over 3–4 weeks	Sedation
Gabapentin	100 mg tid	Increase by 100 mg tid every 3 days to goal dose of 600–1200 mg tid	Sedation, ataxia, peripheral edema
Levetiracetam	500 mg bid	Increase to 1000 mg bid as needed	Sedation, ataxia
Topiramate	25 mg qd	Increase by 25 mg qd each week to goal dose of 100–200 mg bid	Weight loss, anomia, nephrolithiasis, acral paresthesias
Zonisamide	50 mg qd	Increase by 50 mg qd each week to goal of 100–200 mg qd	Nephrolithiasis, weight loss

[a]First-line agent

outstretched. Kayser-Fleischer (KF) rings, brownish-green copper deposits in the Descemet membrane of the cornea, are the tell-tale physical examination sign of Wilson disease. If not visible by simple visual inspection, slit-lamp examination may help detect KF rings. The characteristic laboratory findings of Wilson disease are reduced serum ceruloplasmin (<20 mg/dL), and elevated urine 24-hour copper excretion (>40 μg/mL) [1]. If clinical suspicion for Wilson disease remains despite normal or equivocal test results, refer the patient for genetic testing or liver biopsy. Treatment with the copper-chelating agents trientine and penicillamine help both the neuropsychiatric and hepatic components of the disease [1]. Wilson disease should be evaluated and treated in conjunction with a hepatologist.

Enhanced Physiologic Tremor

Every person has a small-amplitude, high-frequency tremor that is usually imperceptible in day-to-day activities. Some patients, however, experience an enhanced physiologic tremor, which has a very high frequency, usually involves the hands, and appears with stress such as performance anxiety. Patients with performance anxiety usually respond to a small dose of propranolol (10–40 mg PRN) prior to anticipated tremor development. Considering treating those who do not respond to propranolol with clonazepam (0.5–1 mg PRN) or lorazepam (0.5–1 mg PRN).

Secondary Tremor

A variety of medications, toxins, and metabolic disturbances lead to a tremor that appears quite similar to essential tremor. Table 14.2 lists common medication culprits. Intoxication with caffeine, cocaine, and phencyclidine and withdrawal from

Table 14.2 Common medications which produce tremor

Neuroleptics
Beta agonists
Theophylline
Lithium
Valproic acid
Cyclosporine
Tacrolimus
Amiodarone
Levothyroxine
Selective serotonin reuptake inhibitors

ethanol and benzodiazepines may also produce tremor. Hyperthyroidism, hypoglycemia, uremia, and hepatic dysfunction are the common medical conditions that may precipitate tremor. Correction of the responsible problem or withdrawal of the offending medication usually results in tremor resolution or improvement.

Resting Tremor

Parkinsonian Tremor

Up to 75% of patients with Parkinson disease will develop a tremor, and it is the most prominent feature in approximately 15% [2]. Parkinsonian tremor is a low-frequency, small-to-medium amplitude, resting tremor which most commonly involves one hand or foot in an asymmetric fashion. It may change in appearance and distribution, even during a single office visit. Classical Parkinsonian tremors include:

- Flexion-extension of the wrist
- Pronation-supination of the wrist
- Pill-rolling involving the thumbs and fingers
- Foot tapping
- Internal-external rotation at the hip
- Up-and-down jaw movements
- Repetitive perioral and nasal muscle contractions (“rabbit tremor”)

Anticholinergic medications such as trihexyphenidyl (0.5–2 mg bid-tid) and benztropine (0.5–2 mg bid) are the mainstays of treatment of parkinsonian tremor and are most useful when tremor is the predominant system. Levodopa and dopamine agonists are less effective treatments for tremor than they are for bradykinesia and rigidity. Deep brain stimulation of the ventral intermediate nucleus of the thalamus or the subthalamic nucleus may help in refractory cases [3]. Treatment of Parkinson disease is discussed in further detail in Chap. 13.

Intention Tremor

Cerebellar Outflow Tremor

Lesions of the dentate nucleus of the cerebellum and its connections within the cerebellum and brainstem produce very striking low-frequency, large-amplitude intention tremor. This tremor may have a postural element but becomes much worse when attempting to reach out for a target. Ataxia and other signs of cerebellar dysfunction usually accompany the tremor. Common pathologies include stroke, demyelination, neoplasm, and trauma. Unfortunately, cerebellar outflow tremor responds poorly to treatment.

Other Tremors

Palatal Tremor

Palatal tremor (also called palatal myoclonus) is a low-frequency tremor of the palatal and pharyngeal muscles. It is usually secondary to a lesion of the Guillain-Mollaret triangle which connects the red nucleus, inferior olivary nucleus, and dentate nucleus. In many cases, the palatal tremor is accompanied by tremor of the extraocular muscles (oculopalatal myoclonus), diaphragm, head, and neck.

Dystonic Tremor

Focal or generalized dystonia is often accompanied by a superimposed tremor that is usually worsened by movement. It may be present in the hands or the neck. Dystonic tremor responds best to treatments for dystonia including trixhexyphenidyl, beta blockers, and botulinum toxin injection.

Neuropathic Tremor

Neuropathic tremor is usually a large-amplitude, low-frequency action tremor. It is most common in patients with demyelinating neuropathies, especially those caused by monoclonal gammopathies (Chap. 15) [4].

Task-Specific Tremor

Some patients develop tremor upon performing a specific task. The most common of these task-specific tremors is primary writing tremor. Treatments for primary writing tremor include specialized writing devices, medications used for essential tremor, and local botulinum toxin injections.

Orthostatic Tremor

This form of tremor is a high-frequency tremor that occurs exclusively in the legs upon standing, often after standing for a minute or two. Clonazepam and gabapentin may be helpful in reducing orthostatic tremor.

Psychogenic Tremor

Psychogenic tremor should be included in the differential diagnosis of any tremor. This may be a resting or action tremor and may have any amplitude or frequency. The tremor improves with distraction and worsens when the patient focuses on it. One feature of psychogenic tremor that may help to distinguish it from other tremors is entrainment: the patient will not be able to continue to feign a tremor in a hand (or other affected body part) when asked to tap out a complex rhythmic pattern with the other hand.

Jerking Movements

Myoclonus

Myoclonus is defined as a sudden-onset, simple, brief-duration jerking movement of a muscle or group of muscles. It is not suppressible. It may be a manifestation of a systemic disease, associated with an epilepsy syndrome, or occur as a benign phenomenon. Essentially any part of the central nervous system may generate myoclonus. Because myoclonus is difficult to classify based on appearance alone, it is usually easier to make a diagnosis based on the signs of accompanying medical or neurological disease:

Toxic and Metabolic Myoclonus

The metabolic disturbances that produce myoclonus include uremia, hepatic encephalopathy, and thyroid dysfunction. Medications that precipitate myoclonus include narcotics, anticonvulsants, antidepressants, calcium channel blockers, and lithium. Correction of the responsible toxic exposure or metabolic abnormality reverses the myoclonus.

Anoxic Myoclonus

Acute Post-anoxic Myoclonus

Many patients in coma following cardiac arrest develop myoclonus, often diffuse and continuous [5]. The myoclonus may be quite violent and disturbing to family members, and may persist despite all efforts short of pharmacologic paralysis. Acute anoxic myoclonus portends a uniformly poor prognosis (Chap. 2) and should prompt serious discussions about the direction of care with family members and intensive care unit physicians.

Chronic Post-anoxic Myoclonus (Lance-Adams Myoclonus)

A patient who *recovers* from anoxic brain injury may develop myoclonus that occurs with movement and is absent at rest. For this reason, it is often called intention myoclonus. Post-anoxic myoclonus is difficult to control but may respond to clonazepam (0.5–2 mg bid), levetiracetam (500–1000 mg bid), or valproate (500–1000 mg bid). Spontaneous improvement may occur.

Myoclonus Associated with Dementia

Myoclonus is often an early feature of Creutzfeldt-Jakob disease (CJD) (Chap. 4). Myoclonus in a demented patient, however, is not pathognomonic for CJD, and may develop in the later stages of any of the degenerative dementias.

Myoclonic Epilepsy

Juvenile myoclonic epilepsy (Chap. 20) is the most common of the epilepsies associated with myoclonus. Progressive myoclonic epilepsies are rare, progressive neurodegenerative disorders including neuronal ceroid lipofuscinosis, Lafora body disease, and myoclonic epilepsy with ragged red fibers (MERRF). They tend to present in childhood, although sometimes they begin in the late teens or early adulthood.

Opsoclonus-Myoclonus

This condition, characterized by opsoclonus (fast, chaotic, multidirectional eye movements) and myoclonus is classically associated with neuroblastoma in children. In adults, opsoclonus-myoclonus may be a paraneoplastic process or may be associated with an inflammatory or autoimmune disorder [6]. Like other forms of myoclonus, opsoclonus-myoclonus often responds to clonazepam or valproate. Adrenocorticotropic hormone infusions are effective in children but tend not to work in adults.

Segmental Myoclonus

Segmental myoclonus involves muscle groups supplied by one or more contiguous segments of the brainstem or spinal cord [7]. It may be misdiagnosed as another abnormal movement, usually tics or hemiballismus. Common causes include strokes, multiple sclerosis, tumors, and encephalomyelitis.

Palatal myoclonus (also discussed above) is one example of a segmental myoclonus in which repeated contractions of the tensor veli palatini produce a rhythmic or jerky oscillation of the palate and a characteristic clicking sound in the ear.

Clonazepam and valproic acid often provide good symptomatic control of segmental myoclonus, but treating the responsible cause is the most important step in therapy.

Physiologic Myoclonus

The two most common examples of physiologic myoclonus are hypnic jerks (sleep starts that occur just upon falling asleep) and hiccoughs (diaphragmatic myoclonus). With rare exception, physiologic myoclonus does not require any further evaluation or treatment.

Essential Myoclonus

Essential myoclonus is a benign condition that begins in childhood or young adulthood and is often inherited in an autosomal dominant fashion [8]. Exhaustive evaluation discloses no underlying structural or metabolic abnormalities. Essential myoclonus improves considerably with ethanol ingestion, which cannot be

recommended as long-term therapy. Many patients are not bothered by their symptoms and some note an improvement over time. For patients with disabling myoclonus, clonazepam is often helpful.

Ballismus

Ballismus is a violent, involuntary flinging movement of a limb that may be difficult to distinguish from myoclonus. It usually involves one side of the body, in which case it is called hemiballismus. Although hemiballismus is classically associated with strokes involving the subthalamic nucleus, this is the lesion site in only a minority of cases, as other subcortical structures are often involved [9]. Hemiballismus is best treated with haloperidol in divided doses up to 15 mg. Most patients need treatment for several months, but in some, the hemiballismus is permanent.

Tics

Tics are repetitive, stereotyped movements of a muscle or group of muscles. They usually begin in childhood and patients with new-onset tics in adulthood often have a prior history of childhood tics that improved for years before re-emerging. Tics may involve the face, limbs, trunk, or voice. Simple tics are brief, jerky movements of a single muscle group while complex tics involve multiple muscle groups and may result in a sustained posture or complex series of movements. Examples of simple motor tics include jerking and blinking. Complex motor tics include touching, scratching, and sustained mouth opening or closing. Simple vocal tics include grunting and throat clearing. Complex vocal tics are formed words and other phrases. Coprolalia is a specific form of complex vocal tic in which patients produce bursts of profanity. There is an urge to have a tic that precedes its expression, and patients with tics can suppress them for short periods of time. Sustained tic suppression, however, may result in a more severe flurry. Tics are often accompanied by neuropsychological problems including attention deficit hyperactivity disorder, obsessive compulsive disorder, and anxiety. Tourette syndrome is a chronic childhood-onset tic disorder in which there are multiple motor tics and at least one vocal tic.

Behavioral therapy is usually the first line of treatment for tic disorders. First-line pharmacologic options for tics include guanfacine, clonidine, and clonazepam. If these are not effective, antipsychotics and the monoamine-depleting agents tetrabenazine or valbenazine may be explored. Deep brain stimulation and botulinum toxin injections may help patients with refractory tics. Addressing accompanying neuropsychological problems is often as important as treating the tics themselves.

Limb-Shaking Transient Ischemic Attacks

Flapping or trembling of an arm may be a manifestation of contralateral carotid artery stenosis, especially during periods of relative hypotension [10]. The episodes may last for seconds or minutes at a time and are sometimes confused with seizures. Correction of the carotid stenosis or prevention of further hypotensive episodes should eliminate limb-shaking TIAs.

Twitching

Fasciculations

Fasciculations are visible muscle twitches that are generated at the level of the motor neuron, nerve root, or peripheral nerve. They may affect the face, eyes, tongue, and limbs. Most patients with fasciculations are otherwise neurologically normal and therefore have a diagnosis of benign fasciculations or cramp-fasciculation syndrome [11]. The association of fasciculations with amyotrophic lateral sclerosis (ALS) (Chap. 10) is widely known, but fasciculations in ALS are not often the presenting symptom of ALS and when they do occur, are accompanied by muscle weakness and wasting. Many patients with ALS are not aware of their fasciculations until a physician points them out. For patients with benign fasciculations, reassurance is often not helpful, and patients may find relief only after undergoing a negative battery of tests, including EMG and sometimes MRI of the brain (despite being counseled that a brain abnormality, in isolation cannot produce fasciculations). Symptoms improve by decreasing caffeine intake, reducing stress, and limiting heavy exercise. If these lifestyle modifications are not effective, benign fasciculations may respond to carbamazepine (200–800 mg bid), gabapentin (300–1200 mg tid), or clonazepam (0.5–1 mg bid).

Twisting and Repetitive Movements

Chorea and Athetosis

Chorea is an irregular, purposeless, twisting or flowing movement. Often, a patient with chorea attempts to incorporate the movement into an intended movement in order to mask the abnormality (parakinesia). Athetosis is a slow, purposeless, writhing movement. These two abnormal movements frequently accompany each other and when this is the case the term "choreoathetosis" is used. Choreoathetoid movements may involve the limbs, face, eyelids, lips, and tongue. They may be difficult to distinguish from dystonia: the main way to differentiate the two is that choreiform movements tend to be more random whereas dystonic movements are more patterned. The following is a brief discussion of some of the more common of the disorders that produce chorea:

Huntington Disease (HD)

HD is an autosomal dominant neurodegenerative disorder which most often presents in young adulthood or early middle age. Symptoms usually begin with mild clumsiness or fidgetiness which evolves over time into full-blown chorea. Some patients present with dementia or with behavioral changes such as impulsivity and irritability. There may be a family history of psychiatric disease or poorly understood early institutionalization and death. As the disease progresses, chorea becomes less prominent: rigidity, bradykinesia, and cognitive decline come to dominate the clinical picture. The diagnosis of HD is made by finding CAG repeat expansion in the HTT gene, which encodes the huntingtin protein. Striatal atrophy with hydrocephalus ex vacuo on MRI (Fig. 14.1) may support the diagnosis, but genetic confirmation is required. Unfortunately, HD is a relentlessly progressive disease, and symptomatic therapy is the mainstay of treatment. Tetrabenazine, valbenazine, deutetetrabenazine, clonazepam, or neuroleptics may help to control the chorea, but as the disease progresses bradykinesia, rigidity, and cognitive symptoms dominate and patients require around-the-clock care, often in a nursing home setting.

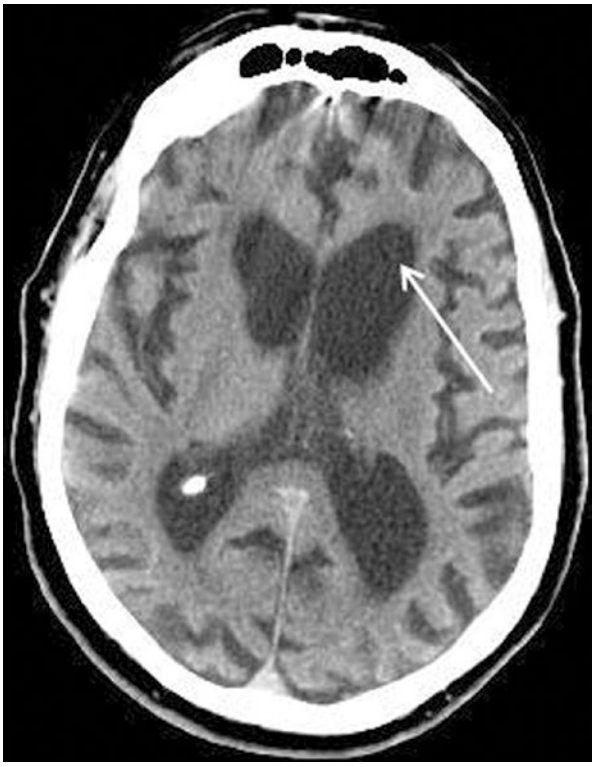

Fig. 14.1 CT scan of the brain in a patient with Huntington disease. Note hydrocephalus ex vacuo, involving particularly the caudate nucleus

Chorea Gravidarum

Chorea may develop during the first or second trimesters of pregnancy. In many cases, an underlying cause such as Sydenham chorea, hyperthyroidism, or the antiphospholipid antibody syndrome may be identified. In other patients, however, there is no identifiable cause and the term chorea gravidarum is used. Although this condition usually resolves spontaneously after several weeks, neuroleptics such as haloperidol may be needed to control disabling symptoms.

Other Causes of Chorea

Medications including dopamine-blocking agents, anticonvulsants, and oral contraceptives may produce chorea. Patients with Wilson disease may develop chorea, amongst other abnormal movements. Sydenham chorea is an autoimmune disorder that occurs in children with rheumatic fever. In rare cases, it may occur for the first time or recur in adults. Other autoimmune disorders that may be associated with chorea include systemic lupus erythematosus and the antiphospholipid antibody syndrome. Stroke, usually in the contralateral basal ganglia or thalamus may produce chorea. Nonketotic hyperglycemia may also lead to unilateral or bilateral chorea and ballismus. Neuroacanthocytosis, hyperparathyroidism, hyperthyroidism, and AIDS are rare causes of chorea.

Dystonia

Dystonia is a movement disorder characterized by twisting, repetitive movements. Dystonia produces torsion or fixation of a body part in a consistent direction, unlike choreoathetoid movements which are in multiple directions and vary from moment to moment. Dystonic movements are often associated with local pain and spasm, and sometimes with a superimposed tremor. They are triggered by movement, worsened by stress, and usually improve during sleep. Many patients have sensory tricks in which touching or stroking a body part affected by the dystonia relieves the contraction briefly. Dystonias may be focal (affecting one body part), segmental (affecting several adjacent body parts), or generalized in distribution. Focal dystonias are the most common types in adults. I will not discuss generalized dystonias in detail, as they are mainly diseases of childhood and adolescence.

Most dystonic disorders are primary, meaning that there are no nervous system abnormalities beyond the dystonia and possibly, a mild tremor. Secondary dystonias are those that are caused by another neurologic disorder or by a structural or metabolic abnormality. Secondary dystonia should be suspected in patients with accompanying neurologic symptoms such as weakness, ataxia, or severe tremor. Although there are many causes of secondary dystonia, focused evaluation including a careful medical history, medication review, MRI of the brain (to look for strokes and mass lesions affecting the basal ganglia), and assessment for Wilson disease and Huntington disease are high-yield investigations. Multigene panels to investigate for genetic sources of dystonia are valuable for younger patients. A comprehensive

discussion of dystonia evaluation is beyond the scope of this text, and the interested reader is referred to a relevant review [12].

Cervical Dystonia (CD)

This is the most common focal dystonia in adults. The head may be twisted in any direction: turned to the side (torticollis), twisted laterally so that the ear approaches or touches the shoulder (laterocollis), bent forward (anterocollis), or bent backward (retrocollis). Simultaneous torsion of the head in multiple planes is common. The severity of CD ranges from subtle rotation of the head which is not obvious to even friends and family members to fixation of the head in one position with unbearable pain and spasm. In some cases, CD is associated with other movement disorders: a classical association is anterocollis with multiple system atrophy [13]. Although agents such as benzodiazepines or baclofen may help slightly, botulinum toxin injections are the most effective treatments for CD. Deep brain stimulation of bilateral globus pallidus may help patients with refractory symptoms [14].

Task-Specific (Occupational) Dystonias

Dystonia, as a rule, is worse with movement. Task-specific or occupational dystonias emerge exclusively when the patient attempts to perform a specific action. Writer's cramp is the most common task-specific dystonia: patients with this condition find that their hand twists or postures when they attempt to write with a pen or pencil. Writing becomes slow, effortful, and painful, and patients resort to using larger and larger pens, writing with their other hand, or typing. The contralateral hand may be affected by milder dystonic movements. Typing, playing musical instruments, and golfing are other tasks associated with dystonia. Some patients may obtain modest symptom relief with trihexyphenidyl, but local botulinum toxin injections are the most effective treatment for task-specific dystonias.

Stiffness and Cramping

Cramps

Cramps are characterized by strong, painful, involuntary muscle contractions. Although patients perceive cramps as being muscular pains, they are generated by the peripheral nerve. Nocturnal cramps, particularly of the calves and foot muscles, are the most common variety. Heavy exercise, dehydration, and electrolyte imbalances may also precipitate cramps. Stretching the affected body part usually improves cramps. In some cases, cramps are a manifestation of a neurogenic disease such as polyneuropathy or amyotrophic lateral sclerosis. For patients with otherwise normal physical examinations, check thyroid function, potassium, magnesium, and calcium, and correct as needed. In most cases, a specific etiology is not identified. Quinine is an effective treatment for cramps but is not widely available due to its potential to cause cardiac arrhythmias. Tonic water contains a small amount of quinine and can help some patients. Medication options for treating cramps include

clonazepam (0.5–1 mg qhs), verapamil (80–120 mg qhs), diphenhydramine (25–50 mg qhs), oxcarbazepine (150–600 mg qhs), and gabapentin (300–600 mg qhs).

Stiff-Person Syndrome

Stiff person syndrome is an uncommon condition characterized by chronically progressive stiffness of the muscles of the trunk and limbs. The axial muscles, particularly the paraspinal muscles, are usually affected most severely, and may cause the patient to adopt an exaggerated hyperextended posture, leading to opisthotonos in severe cases. Other patients first develop asymmetric symptoms in one leg or foot. Approximately 70% of patients will have antibodies to glutamic acid decarboxylase [15]. Rare patients have antibodies to amphiphysin, gephyrin, or the glycine receptor [16–18]. Patients with stiff person syndrome often have other autoimmune disorders such as diabetes or pernicious anemia. Treatment options include diazepam (up to 10 mg tid) and baclofen, given orally (40 mg bid) or via intrathecal pump in refractory cases. Periodic intravenous immunoglobulin infusions help some patients [19].

Myotonia

Myotonia is the impaired relaxation of a muscle after voluntary contraction or percussion. A patient with myotonia may complain of disabling muscle stiffness with exercise or cold. Other patients, however, have very mild myotonia and are not bothered by it. There are several common patterns of myotonia. Hand grip myotonia is the failure to release the grip after a vigorous hand shake. Eyelid myotonia is the failure to open the eyelids after they are squeezed shut. Percussion myotonia is elicited by briskly striking the thenar eminence, long finger extensors in the forearm, deltoid, or tongue with a reflex hammer. If physical examination fails to reveal myotonia, it may be demonstrated electromyographically, especially upon muscle contraction or cooling.

Myotonic Dystrophy

Myotonic dystrophy is an autosomal dominant, multisystem disorder characterized neurologically by myotonia, muscle weakness, and in some cases, mental retardation. Cardiac conduction block and cataracts are common systemic features which are more important than the neurologic aspects of the disease. A patient with myotonic dystrophy characteristically has a long face, frontal baldness, temporal wasting, and ptosis. Patients with DM1 have predominantly distal weakness and more multisystem organ involvement. Those with DM2 have predominantly proximal weakness and milder extramuscular disease. Genetic testing is available to confirm both DM1 and DM2. Phenytoin (100 mg tid) or mexiletine (200–400 mg tid) may help problematic myotonia, but in general, this symptom is not bothersome for these patients. Most patients with myotonic dystrophy, particularly DM1 will require

multiple physicians. Of greatest importance are a cardiac electrophysiologist to address the potential for cardiac arrhythmia and the need for pacemaker placement and an ophthalmologist for evaluation and treatment of cataracts and ptosis.

Myotonia Congenita and Paramyotonia Congenita

Myotonia congenita is an inherited disorder characterized by myotonia in the first few seconds or minutes of exercise or movement that improves with continued activity. It is often first noted when a child begins to play sports. Muscle stiffness usually improves after warming up. Myotonia congenita has both autosomal dominant (Thomsen disease) and recessive (Becker disease) forms caused by mutations in the chloride channel CLCN1. The recessive form may be associated with mild muscle weakness. Mexiletine (200–400 mg tid) is often helpful but must be used cautiously as it may lead to cardiac arrhythmias. Phenytoin and carbamazepine may be useful for patients who do not respond to or do not tolerate mexiletine.

Paramyotonia congenita also develops in youth and is characterized by myotonia that paradoxically worsens with continued activity and with cold exposure. It is caused by mutations in the sodium channel SCN4A and can be treated with mexiletine or acetazolamide.

Abnormal Facial Movements

Myokymia

Myokymia is a rippling, undulating muscle movement that is physiologically composed of spontaneous, rhythmic or semirhythmic motor unit discharges. Myokymia may manifest itself in the limb muscles (usually in association with neuropathic disorders and especially in the setting of radiation-induced plexopathies) or in the facial muscles. Facial myokymia is usually secondary to an ipsilateral pontine tegmental lesion, particularly multiple sclerosis. When an acute inflammatory lesion is the cause, it typically lasts for only a few weeks at a time. Patients with disabling, persistent symptoms may benefit from botulinum toxin injections, carbamazepine, or phenytoin [20].

Oromandibular Dystonia

Oromandibular dystonia is characterized by a variety of abnormal facial movements including jaw clenching, mouth opening, and facial grimacing. In severe cases, these movements impair speech and swallowing. Oromandibular dystonia frequently involves the orbicularis oculi (in which case the combination is called Meige syndrome) and the adjacent neck and shoulder muscles. Similar to other focal dystonias, oromandibular dystonia responds to directed botulinum toxin injections.

Hemifacial Spasm

Hemifacial spasm is the intermittent, unilateral twitching of both the upper and lower halves of the face. It may be present at rest but is more often triggered by facial movements. The cause of hemifacial spasm is believed to be microvascular compression of the facial nerve as it emerges from the brainstem. MRI of the brain with thin cuts through the brainstem should be performed to exclude a structural lesion. Treatment with anticonvulsants such as carbamazepine may help slightly, but most patients require botulinum toxin injections. In some refractory cases, surgical decompression of the facial nerve is necessary, though this procedure places the patient at risk for facial palsy.

Tardive Dyskinesia (TD)

TD is a group of movements including tics, chorea, athetosis, and dystonia that result from treatment with antipsychotics or the antiemetic metoclopramide. Orofacial dyskinesias such as chewing, puckering, grimacing, and repetitive eye closure are among the most easily recognizable varieties. TD may also affect the limbs, neck, trunk, and even the diaphragm. The movements are present continuously and may be very disabling. Symptoms usually develop after more than 5 years of taking the responsible drug, though they may also begin after shorter exposures, sometimes even a few months. TD is more likely to result from treatment with older antipsychotics such as haloperidol or fluphenazine than with one of the newer atypical agents such as risperidone or olanzapine, though the risk with the newer antipsychotics is not zero. TD is often difficult to treat. The first step is to discontinue the responsible medication or taper it to its minimal effective dose, keeping in mind that this may make TD symptoms worse for several weeks. For patients who are taking one of the older antipsychotics, switching to clozapine or quetiapine may help. In patients for whom changing or discontinuing antipsychotics does not work or is not possible, clonazepam (0.5–2 mg bid) may reduce TD symptoms. The dopamine-depleting agents tetrabenazine, valbenazine, and deutetetrabenazine also useful in patients with debilitating symptoms. In some patients, resuming high-potency antipsychotics may paradoxically improve TD. Few patients with TD achieve a complete remission.

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Distal and Generalized Sensory Symptoms

15

Overview of Sensory Symptoms

Pain is the sensory symptom that most frequently brings a patient to neurologic attention. The first step in evaluating pain is to determine its character. Neuropathic pain has sharp, burning, or electrical qualities. Nociceptive pain, by comparison, has dull and aching qualities. Pain due to vascular insufficiency is most often described as coldness or freezing. In general, pain may be divided into focal (Chap. 16) and generalized or distal-predominant (this chapter) in distribution. Because patients may report only the most prominent location of symptoms, you must inquire specifically about pain involving the face, scalp, trunk, back, arms, hands, groin, legs, and feet.

Numbness is the second important symptom of sensory dysfunction. When patients use the term numbness, they may mean one of several different sensations: a lack of feeling or deadness; a sensation that the affected body part is covered by something such as a glove, sock, or extra layer of the skin; or a sensation that the body part is asleep. Some patients will report that their socks are bunched up around their feet, that they are walking on sponges, or that the hands or feet are buried in cement. Be aware of the common, erroneous description of limb weakness as numbness.

Paresthesia is a sense of tingling, pins and needles, abnormal vibration, or a feeling that a body part is asleep. Some patients with paresthesia may describe it initially as pain or numbness, and an accurate description of the problem may be obtained only by specifically asking about a perception of pins and needles. Paresthesia is more specific for neurologic dysfunction than any other sensory symptom.

There are several abnormal sensations that are due to motor dysfunction. The most common of these are cramps, twitching (fasciculations), and restlessness.

It is important to note that because sensory symptoms are entirely subjective, they can be feigned or exaggerated quite easily. Important clues to factitious sensory symptoms include a large number and variety of symptoms, requests for narcotic

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medications or completion of disability paperwork at an initial office visit, and a lack of a plausible anatomic distribution of symptoms.

Sensory System Anatomy

Pain and temperature sensations from the limbs and trunk are mediated by small-diameter nerve fibers. These fibers travel through the nerves and nerve roots, reaching their cell bodies in the dorsal root ganglia. After entering the spinal cord, pain and temperature fibers ascend one or two segments before decussating in the ventral white commissure. They ascend through the spinal cord in the spinothalamic tract, eventually reaching the ventroposterolateral nucleus of the thalamus. These fibers from the thalamus project to the insula.

Vibratory and proprioceptive sensations are mediated by large-diameter nerve fibers. These fibers also travel through the nerves and nerve roots to reach cell bodies in the dorsal root ganglia and enter the spinal cord. Within the spinal cord, fibers from the lower extremity travel through the gracile fasciculus, while those from the upper extremity travel through the cuneate fasciculus. These fibers reach the gracile and cuneate nuclei in the medulla and decussate in the medial lemniscus. Lemniscal fibers synapse in the ventroposterolateral nucleus of the thalamus and project to the primary sensory cortex of the postcentral gyrus.

Sensory Examination

Sensory examination should include tests of pinprick, vibration, position sense, and cortical modalities.

Pinprick and Temperature Sensation

Pinprick examination of every square inch of the skin is time-consuming and leads to a great deal of extraneous and sometimes misleading information. There are several strategies that improve both the diagnostic yield and efficiency of this portion of the sensory examination. First, take a thorough history in order to get a sense of the likely distribution of sensory deficits. The examination of a patient with a probable length-dependent polyneuropathy requires a different strategy than the examination of a patient with a mononeuropathy or monoradiculopathy. It is often quite helpful to ask the patient to trace the area of cutaneous sensory loss before initiating the sensory examination. When testing pinprick, begin by examining a completely normal area to establish that the patient can perceive the sharp sensation of a pinprick accurately. Next, test an area that is suspected to be abnormal based on the information gained from the history and march the pin from the abnormal area back into the normal area. For example, in a patient with a suspected length-dependent polyneuropathy, begin distally at the toes to see whether the patient can detect the

pinprick and then march the pin proximally, determining where the patient first perceives the sensation properly. More subtle deficits require a different technique. In a patient with mild sensory abnormalities, it is helpful to compare the symptomatic body part to a control body part. For example, when testing a patient with a possible right L5 radiculopathy, poke the dorsum of the left foot with the pin and tell them that this sensation is 100%. Next, poke the dorsum of the right foot and ask the patient to assign a percentage to the strength of this sensation. When examining pinprick for the purposes of a screening examination, establish that sensation is preserved by testing two or three pinpricks in each dermatome and nerve distribution (Fig. 15.1).

Because pinprick and temperature perception are both mediated by small-diameter nerve fibers, examining temperature usually does not add much new information to the neurologic examination. False-positive cold sensation testing is frequent in patients with cold extremities. In addition, it may be difficult to find standardized cold and warm stimuli. Despite these limitations, if pinprick sensation is entirely preserved and there is a high index of suspicion for small-diameter nerve fiber dysfunction, testing perception of warmth and coldness may help to disclose an important deficit. Temperature testing is also useful for patients who do not tolerate or cannot accurately report the results of the pinprick examination.

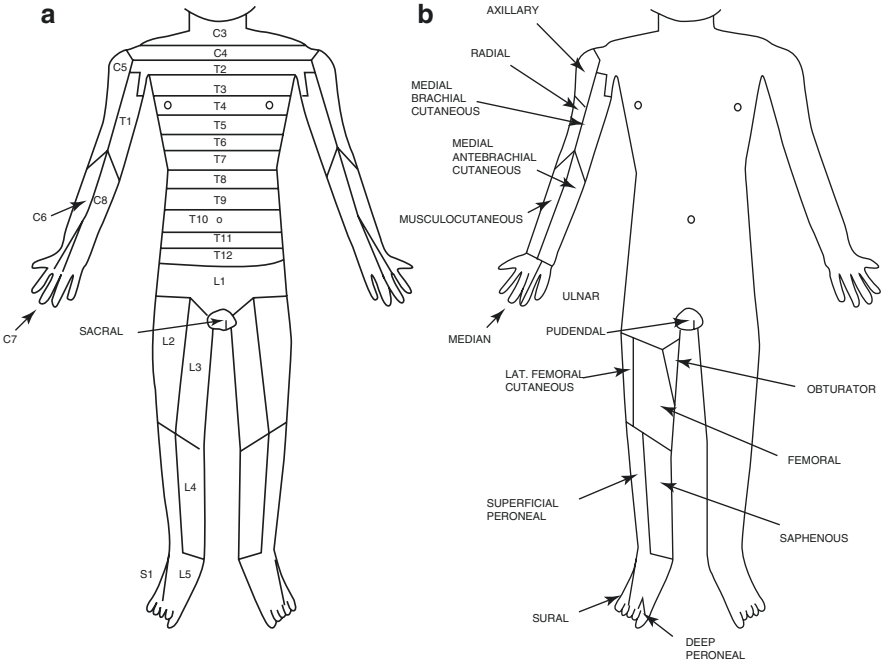

Fig. 15.1 Cutaneous sensory distributions of (**a**) the nerve roots and (**b**) individual nerves on the ventral surface of the body. Note in particular the T2 (axilla), T4 (areolae), and T10 (umbilicus) dermatomes. See Chap. 16, Fig. 16.1 for additional details on the innervation of the hand

Vibratory and Joint Position Perception

Examine vibratory sensation with a 128-Hz tuning fork. Absence of vibratory perception at the great toe is clearly abnormal. If the patient cannot appreciate vibration at the great toe, move the tuning fork to the medial or lateral malleolus, to the knee, and then to the sternum until they feel the vibration. The normal duration of tuning fork perception is not clearly defined. Some use the very restrictive criterion that both patient and doctor should feel the vibratory perception for the same length of time. Others use cutoffs such as 10 or 12 seconds of vibratory perception at the great toe. Because none of the techniques for vibratory perception have been standardized, experimentation is necessary to establish a personal standard of normal and abnormal. My technique involves striking the tuning fork vigorously so that its heads hit each other and then placing the base of the tuning fork on the interphalangeal joint of the great toe. Using this technique, the approximate number of seconds of vibratory perception at the great toe may be computed for by subtracting the first digit of the patient's age from 16. For example, a 49-year-old patient should have 12 seconds of vibratory perception at the great toe.

Joint position examination generally offers little more information beyond what is obtained by testing vibratory perception. To test joint position, instruct the patient to close their eyes and tell them that you will move their great toe either upward or downward. Grasp the toe by the sides (not by the top and bottom) and move it by no more than 5 mm. Normal subjects should be able to detect this movement reliably.

Cortical Sensory Modalities

The most commonly tested cortical sensory modalities are graphesthesia, stereognosis, and two-point discrimination. These higher-order sensory functions are considered functions of the contralateral parietal lobe. Accurate testing of these modalities may occur only when the patient has otherwise preserved gross touch and pinprick sensation. Test graphesthesia by instructing the patient to close their eyes and then asking them to interpret a number that you trace on their palm. Trace at least five different numbers (2, 3, 6, 7, and 8 are the most straightforward ones to interpret) on one palm and compare the results to the other palm. Test stereognosis by asking the patient to distinguish between a quarter, dime, and nickel placed in each hand. Most patients can do this easily. Finally, test two-point discrimination by placing the tips of a caliper against the patient's skin. Determine whether they can discriminate between one point and two points separated by 5–10 mm. Abnormal graphesthesia, stereognosis, and two-point discrimination point to dysfunction in the contralateral parietal lobe but should not be judged too strictly, as false-positive test results are common.

Polyneuropathy: Length-Dependent

Polyneuropathy is a pathologic process which by definition involves all the nerves in the body. It is exceedingly rare, however, for all of the nerves to be clinically involved at disease onset or even at any subsequent point. Polyneuropathy is most often a length-dependent process and symptoms develop in a slowly progressive, somewhat stereotyped fashion. The classic initial complaints of polyneuropathy are numbness, tingling, and pain which begin in the toes and spread more proximally over months to years. When symptoms reach the knees, nerves of equivalent length in the fingertips and hands become involved. By the time the elbows are involved, symptoms are present in the midline of the trunk. In patients with severe neuropathy, only small patches of sensation over the vertex of the head and along the spine are preserved. Symptoms usually do not progress to this extent, and many patients have symptoms confined to the feet and distal legs for many years.

Most patients with polyneuropathy have mostly or exclusively sensory symptoms at onset. Motor symptoms may be minor and go unnoticed. Imbalance is often a problem at presentation (Chap. 18). To elicit a history of balance problems, ask the patient whether they feel as if they are going to fall when they close their eyes in the shower or whether it is difficult for them to keep their balance if they get up at night to use the bathroom.

There are several other important physical examination findings in patients with length-dependent polyneuropathy. Visual inspection may disclose wasting of the intrinsic muscles of the feet, clawing of the toes with high arches, and wasting of the distal legs suggestive of Charcot-Marie-Tooth disease. Bear in mind, however, that any distal-predominant polyneuropathy may cause muscle wasting. The most obvious foot muscle in which wasting may be detected is extensor digitorum brevis, the small spherical muscle that is palpable over the proximal dorsolateral foot. Polyneuropathy may also lead to reduced hair growth over the distal legs. Patients with early polyneuropathy usually have little weakness, but when it is present, it is subtle and involves toe extension and flexion. Deep tendon reflexes may be lost or reduced. On sensory examination, patients with polyneuropathy have a combination of pinprick and vibratory loss as described above. The term “stocking-glove sensory loss” is often used to refer to involvement of the distal before the proximal extremities. Testing for a Romberg sign, described further in Chap. 18, is also important in polyneuropathy.

Polyneuropathy: Non-length-Dependent

Although length-dependent sensorimotor polyneuropathy accounts for the majority of polyneuropathies in clinical practice, many diagnoses will be missed if only this pattern is considered. Polyneuropathies with predominantly motor manifestations include chronic inflammatory demyelinating polyneuropathy (Chap. 10) and multifocal motor neuropathy with conduction block (Chap. 11). Rapidly progressive polyneuropathies are discussed in Chap. 12. Some uncommon causes of

polyneuropathy such as Tangier disease, lead toxicity, and porphyria may produce predominantly proximal rather than distal symptoms. Neuropathies associated with prominent ataxia include vitamin E deficiency, Sjogren syndrome, and certain variants of Charcot-Marie-Tooth disease. Ganglionopathy is an uncommon pattern of neuropathy that produces sensory symptoms in an asymmetric fashion, often worse in the upper than the lower extremities. Common sources of ganglionopathy include Sjogren syndrome, vitamin B_6 toxicity (most often producing symptoms when used in conjunction with isoniazid for the treatment of tuberculosis), and the anti-Hu antibody syndrome.

Evaluation of Polyneuropathy

Laboratory Screening

Polyneuropathy is caused by a wide variety of medical disorders. In the absence of a relevant past medical history or clear clinical clues to the presence of one of these underlying disorders, a screening battery should consist of a restricted number of high-yield tests (Table 15.1).

Electromyography (EMG) and Nerve Conduction Studies (NCS)

The purposes of EMG and NCS are to confirm the presence of a polyneuropathy, to determine its severity, and to distinguish between axonal and demyelinating forms. Although localization of sensory complaints to the peripheral nerves is often straightforward, diagnostic mimics including disorders of the central nervous system, polyradiculopathy, and psychogenic disorders make EMG and NCS helpful in confusing cases. While neuropathy severity is often obvious from clinical history and examination, electrodiagnostic studies may offer insight into disease severity which becomes important when determining appropriate treatment. Distinguishing between axonal and demyelinating pathologies is perhaps the most important role of EMG and NCS. Axonal polyneuropathies are characterized by decreased response amplitudes with normal or mildly reduced conduction velocities, whereas demyelinating polyneuropathies are characterized by relatively preserved response amplitudes and severe slowing of conduction velocities. The distinction between

Table 15.1 Screening panel for common causes of polyneuropathy

Hemoglobin A_{1c} % and 2-hour oral glucose tolerance test
Thyroid stimulating hormone
B_{12} levels (homocysteine and methylmalonic acid levels if B_{12} level is borderline low)
Serum protein electrophoresis, immunofixation, and urine protein electrophoresis
Blood urea nitrogen and creatinine
Alanine transaminase and aspartate transaminase
HIV antibodies

these two sites of nerve pathology is important, as demyelinating polyneuropathies often respond to immunomodulatory therapy while axonal polyneuropathies do not. EMG and NCS should be employed judiciously, as their sensitivities and specificities are both limited. Because NCS assesses only large-diameter nerve fibers, it is frequently normal when pain (mediated by small-diameter nerve fibers) is the only symptom. Although many EMG studies offer little in the way of additional diagnostic information for polyneuropathy, the following factors always prompt me to order EMG:

- Asymmetric symptom onset
- Proximal symptom onset
- Rapid symptom progression
- Patient age less than 50 years
- Foot deformities suggestive of inherited neuropathy
- Prominent motor signs
- Suspected demyelinating polyneuropathy

Nerve Biopsy

Sural nerve biopsy may offer additional diagnostic information for several uncommon etiologies of polyneuropathy including vasculitis, amyloidosis, tuberculosis, and sarcoidosis. In most cases, nerve biopsy shows nonspecific axon loss which offers little diagnostic information beyond what is provided by the clinical examination and electrodiagnostic studies. Skin-nerve biopsy with measurement of intraepidermal nerve fiber density may help to confirm the diagnosis of a small-fiber neuropathy but does not help to determine an etiology. Its utility in clinical practice is limited by a high false-positive rate.

Etiologies of Polyneuropathy

A detailed discussion of the vast number of causes of polyneuropathy can and does fill a multivolume textbook [1]. The following is a summary of some of the most common and important causes of polyneuropathy:

Diabetes Mellitus

Diabetes mellitus is the most common cause of polyneuropathy in the United States. It may take many forms, including a length-dependent sensorimotor polyneuropathy, a painful small-fiber polyneuropathy, diabetic thoracic radiculopathy (Chap. 17), diabetic amyotrophy (Chap. 16), mononeuropathy multiplex (Chap. 11), or a syndrome which resembles chronic inflammatory demyelinating polyneuropathy (Chap. 10). Although elevated blood hemoglobin A_{1c} percentages are often used to

confirm the presence of diabetes in patients with suspected diabetic neuropathy, oral glucose-tolerance testing is more sensitive [2]. Because diabetes is so common, it is important to not wear blinders by assuming that diabetes is the sole explanation for neuropathy in a diabetic patient: always conduct a thorough evaluation to exclude other reversible causes. Tight glycemic control may arrest progression of neuropathy symptoms but reverses symptoms only rarely. Strict and rapidly achieved euglycemia may lead to "insulin neuritis" or treatment-related diabetic neuropathy in which neuropathy symptoms, particularly severe pain, worsen within 2 months of establishing better blood sugar control [3]. In most cases, agents for neuropathic pain are the mainstay of therapy. Treatment with α-lipoic acid (600 mg qd-tid) may help some patients [4]. One important component of diabetic neuropathy care is prevention of foot ulcers with properly fitting shoes, careful daily foot examinations, and periodic podiatric assessments.

B_{12} Deficiency

B_{12} deficiency may affect the brain, optic nerves, spinal cord, and peripheral nerves. In a small percentage of patients, the peripheral nerves are affected in isolation. Because the spinal cord is involved in up to 90% of cases with neurologic involvement, B_{12} deficiency is discussed further in Chap. 17 [5].

Monoclonal Gammopathy

Monoclonal proteins are circulating immunoglobulins formed from heavy (IgM, IgG, and IgA) and light (kappa or lambda) chains [6]. Monoclonal gammopathy is especially common in older people, and its association with multiple myeloma is well-known. Monoclonal proteins may produce neuropathy by cross-reacting with peripheral nerve antigens, but in other cases, the precise mechanism of neuropathy is not entirely clear. Neuropathies associated with monoclonal gammopathies include:

- Monoclonal gammopathy of undetermined significance (MGUS) producing length-dependent axonal polyneuropathy
- Multiple myeloma associated with axonal polyneuropathy
- POEMS (*P*olyneuropathy, *O*rganomegaly, *E*ndocrinopathy, *M*onoclonal gammopathy, *S*kin changes), a severe demyelinating polyneuropathy associated with osteosclerotic myeloma
- Anti-MAG (myelin-associated glycoprotein) neuropathy, a demyelinating polyneuropathy characterized electrophysiologically by markedly prolonged distal motor latencies
- Waldenstrom macroglobulinemia associated with a sensory or sensorimotor polyneuropathy
- Amyloidosis, a multisystem disorder that usually produces an exquisitely painful neuropathy with prominent autonomic dysfunction

In order to ensure the highest yield for detecting monoclonal gammopathy in patients with neuropathy, request not only serum protein electrophoresis but also immunofixation and 24-hour urine collection for protein electrophoresis [7]. Patients with MGUS should undergo evaluation for multiple myeloma including skeletal survey, calcium level measurement, and hematologic referral for consideration of bone marrow biopsy. In many cases MGUS is simply followed over time as it does not tend to produce a severe neuropathy or lead to identification of a malignancy or other autoimmune disorder. Neuropathy secondary to a monoclonal gammopathy may respond to immunosuppressive and chemotherapeutic regimens, which should be designed in conjunction with a hematologist.

Vasculitis

Vasculitic neuropathies are discussed further in Chap. 11. Although mononeuropathy multiplex is the best known type of vasculitic neuropathy, many patients with vasculitis have length-dependent polyneuropathies or overlapping patterns with features of both length-dependent polyneuropathy and mononeuropathy multiplex.

Ethanol

Polyneuropathy secondary to chronic heavy ethanol use is most likely secondary to a combination of direct toxic effects from the ethanol and from thiamine deficiency: there is considerable debate as to which factor is more important [8]. Discontinuing ethanol consumption and ensuring adequate nutrition may result in modest symptom improvement.

Charcot-Marie-Tooth Disease

Charcot-Marie-Tooth (CMT) disease is the most common inherited polyneuropathy. Wasting, weakness, and areflexia in the lower extremities usually begin in childhood or adolescence. As the disease progresses, atrophy begins in the lower part of the legs giving them an "inverted champagne bottle" appearance. Patients also develop joint deformities. The most common form of CMT is CMT1A, an autosomal-dominantly inherited demyelinating polyneuropathy caused by a duplication of the PMP-22 gene. There are a wide variety of other phenotypes of CMT, each associated with distinct gene mutations [9]. CMT2 is perhaps the most important of these in adults, as it causes a length-dependent axonal polyneuropathy which may mimic more common causes of polyneuropathy. CMT2 is usually distinguished from other axonal polyneuropathies by the presence of severe or predominant motor symptoms or a family history of neuropathy [10]. Many forms of CMT resemble each other quite closely, and it is often not possible to distinguish among them. Genetic testing panels for multiple CMT genes enable pinpointing the specific mutation in many cases. The mainstay of CMT treatment is referral to an orthopedic

and podiatric surgeon for correction of foot deformities. Unfortunately, there is no specific cure for the neuropathy.

HIV

Approximately 50% of patients with HIV, usually those with advanced disease, develop a length-dependent polyneuropathy, often with prominent pain [11]. HIV may also cause a variety of other peripheral nerve problems including chronic inflammatory demyelinating polyradiculoneuropathy and mononeuropathy multiplex. Highly active antiretroviral therapy and pain control are the mainstays of treatment.

Thyroid Dysfunction

Because thyroid function is tested so commonly by primary care physicians, new diagnoses of neuropathy related to thyroid disease are rare in neurologic practice. Nonetheless, thyroid dysfunction is an important cause of neuropathy because it is reversible. Neuropathy usually takes a length-dependent form and occurs more commonly in patients with hypothyroidism than in those with hyperthyroidism [12].

Medication-Induced Neuropathies

A variety of medications may lead to polyneuropathy (Table 15.2).

Idiopathic Polyneuropathy

After extensive screening, many patients with polyneuropathy still lack an identifiable cause. Patients with idiopathic polyneuropathy tend to have mild disease that progresses slowly over years. While there is no specific treatment to reverse

Table 15.2 Medications which may produce polyneuropathy

Chemotherapeutic agents:
Cisplatin
Docetaxel
Oxaliplatin
Paclitaxel
Suramin
Thalidomide
Vincristine
Amiodarone
Chloroquine
Colchicine
Disulfiram
Metronidazole
Phenytoin
Pyridoxine

idiopathic polyneuropathy, patients do get symptomatic relief from agents for neuropathic pain.

Treatment of Neuropathic Symptoms

Sensory symptoms fall into two classes: positive symptoms in which there is an emergence of an abnormal sensation (e.g., pain or paresthesias) and negative symptoms in which sensorimotor function is attenuated or lost (e.g., numbness or weakness). Broadly speaking, medications are available to mask positive symptoms, but unless a reversible cause is identified, there are few treatments for negative neuropathic symptoms. Agents available to treat neuropathic pain and paresthesias are summarized in Table 15.3. Note that because all the oral medications work by

Table 15.3 Medications used to treat neuropathic pain

Medication	Class	Initial dose	Typical effective dose	Side effects
Gabapentin[a]	Anticonvulsant	100–300 mg tid	300–1200 mg tid	Peripheral edema
Pregabalin[a]	Anticonvulsant	50 mg bid	50–300 mg bid	Nausea, weight gain, fatigue
Carbamazepine	Anticonvulsant	100 mg tid	100–200 mg tid	Drowsiness, dizziness, rash, hyponatremia, agranulocytosis
Amitriptyline	Tricyclic antidepressant	25 mg qhs	50–100 mg qhs	Dry mouth, constipation, cardiac arrhythmias
Nortriptyline[a]	Tricyclic antidepressant	25 mg qhs	50–100 mg qhs	Dry mouth, constipation, cardiac arrhythmias
Duloxetine	Serotonin-norepinephrine reuptake inhibitor	30 mg qd	30–60 mg qd	Nausea, dizziness, drowsiness
Venlafaxine	Serotonin-norepinephrine reuptake inhibitor	75 mg qd	150 mg qd	Nausea, dizziness, drowsiness
Tramadol	Weak opioid agonist, serotonin-norepinephrine reuptake inhibitor	50 mg bid	50–150 mg bid	Sedation, may interact with selective serotonin reuptake inhibitors
Methadone[b]	Long-acting opioid	5 mg tid	5–20 mg tid	Addiction potential, constipation, tolerance
Fentanyl patch[b]	Long-acting opioid	25 μg q72h	25–100 μg q72h	Addiction potential, constipation, tolerance
Capsaicin cream	Substance P depleting agent	Topical	---	Burning at application site, effect limited to site of application
Lidocaine patch or cream	Sodium-channel blocker	5% patch qd or cream tid	5% patch qd or cream tid	Effect limited to site of application

[a]Preferred initial agent
[b]Should be reserved for patients with refractory symptoms

reducing the firing of abnormal nerve impulses, the firing of normal ones may also be suppressed, leading to sedation and other cognitive side effects.

Other Causes of Distal Sensory Symptoms

Spine Disease

Both lumbosacral polyradiculopathy and cervical myelopathy may produce lower extremity symptoms that mimic length-dependent polyneuropathy. Compression of the L5 and S1 nerve roots may lead to pain, numbness, and tingling in the feet that is unaccompanied by back pain on occasion. Examination usually shows some asymmetry which helps to make the distinction, but in some cases, nerve conduction studies and needle electromyography are required to make the diagnosis. Cervical myelopathy may also produce distal paresthesias and numbness and should be considered when the hands are more involved than the feet, when pain is absent, or when hyperreflexia and spasticity are present on examination. Both medical and surgical causes of cervical myelopathy may produce a pseudopolyneuropathic presentation. Further evaluation of patients with cervical myelopathy is described in Chap. 17.

Plantar Fasciitis

Inflammation of the plantar fascia is a source of foot pain that may mimic polyneuropathy when it is bilateral. Wear and tear damage to the plantar fascia is particularly common in obese people and in runners and leads to pain which is most severe with the first steps in the morning. Pain is most often centered at the medial calcaneus but may involve the entirety of the sole. On physical examination, the pain of plantar fasciitis may be reproduced by dorsiflexing the toes and palpating the plantar fascia. Treat plantar fasciitis with nonsteroidal anti-inflammatory medications, gentle physical therapy, and, in refractory cases, local steroid injections. Although patients should avoid activities that precipitate pain, it is usually impractical for patients to comply with instructions to stay off of their feet.

Tarsal Tunnel Syndrome

The tarsal tunnel is formed by connective tissue posterior to the medial malleolus. The tibial nerve passes through the tarsal tunnel as it reaches and innervates the sole. Compression of the tibial nerve within the tarsal tunnel, therefore, may lead to numbness, pain, and paresthesias in the bottom of the foot. Tarsal tunnel syndrome should not be considered the lower extremity analog of carpal tunnel syndrome (Chap. 16), because it is quite uncommon and occurs almost always in the setting of serious ankle trauma rather than as a gradual-onset process secondary to overuse.

Polyneuropathy and plantar fasciitis are more likely explanations for symptoms in patients referred for tarsal tunnel syndrome. Signs on examination include numbness in the sole of the foot and paresthesias reproduced by percussing the tibial nerve just posterior to the medial malleolus. Be aware that sensation over the sole is frequently decreased due simply to the thickness of the overlying skin rather than to any specific neuropathology, so pinprick examination abnormalities must be interpreted cautiously. Electrodiagnostic studies show slowing of tibial nerve conduction studies across the ankle but are frequently non-diagnostic, particularly in patients with underlying polyneuropathy. Surgical release of the tibial nerve at the tarsal tunnel may cure the condition, though most tarsal tunnel releases performed in practice are not helpful because the misdiagnosis rate is high.

Morton Neuroma

Morton neuroma is a benign tumor of the plantar nerve. Patients characteristically develop pain and paresthesias in the plantar surfaces of two adjacent toes (e.g., lateral half of digit three and medial half of digit four) which worsen with pressure and wearing shoes. Symptoms may be reproduced by applying pressure directly to the plantar nerve. Morton neuroma should be evaluated and treated by an orthopedist or podiatrist.

Cramps

Cramps are tight, squeezing pains which most commonly occur in the calves and feet and have a tendency to be worse at night. They are discussed in greater detail in Chap. 14.

Restless Legs Syndrome (RLS)

RLS (also known as Willis-Ekbom disease) is a syndrome of unclear etiology characterized by a sensation of discomfort in the lower extremities that occurs at rest, particularly in the early evening when relaxing or while trying to fall asleep. Patients with RLS describe abnormal crawling, itching, or pulling below the knees and feel that they need to move their legs or walk around in order to get relief. There is often a family history of RLS, and women tend to be affected more often than men. The diagnosis is easily established from the clinical history alone. Although a variety of medical conditions may be associated with restless legs syndrome, iron-deficiency anemia is the most common identifiable cause. Patients with ferritin levels less than 50 μg/L should be treated with iron supplementation [13]. Caffeine and nicotine exacerbate restless legs syndrome and should be avoided before bedtime. Gabapentin (100–600 mg qhs) or pregabalin (50 mg qhs to start, titrated up to 300 mg qhs) are the preferred first-line options for most patients. Dopamine agonists such as

pramipexole (initiated at 0.125 mg qd, increased by 0.125 mg qd every 2–3 days up to 0.75 mg qd as needed) or ropinirole (0.25 mg qd, increased by 0.25 mg qd every 2–3 days up to 2 mg qd as needed) given approximately 2 hours prior to anticipated symptom onset are also useful. Dopamine agonists, however, are more likely than gabapentin or pregabalin to produce augmentation, in which symptoms appear progressively earlier and earlier in the day [14]. For patients with augmentation, problems only worsen when doses of pramipexole or ropinirole are escalated. Replacing dopaminergic agents with non-dopaminergic ones is the most effective strategy for treating augmentation. Other medications that may be effective for RLS include levodopa, benzodiazepines, carbamazepine, diphenhydramine, or even low doses of mild narcotics such as codeine.

Raynaud Phenomenon

Raynaud phenomenon is a very common condition caused by low blood flow to the tips of the fingers and toes. It is diagnosed when the skin of the tips of the digits undergoes a biphasic color change (at least two of pallor, erythema, and cyanosis) [15]. Although these color changes are the defining features of Raynaud phenomenon, patients may be referred for evaluation of neuropathy when the most prominent complaints are tingling, burning pain, or numbness. The first step in treating Raynaud phenomenon is to counsel the patient to avoid the cold or to wear gloves or socks when exposed to cold, though most patients have tried these techniques before consulting with a neurologist. The calcium channel blockers (e.g., nifedipine 30–180 mg qd) and topical nitroglycerin theoretically produce vasodilation, but unfortunately, these agents provide only marginal symptom relief, and potential side effects outweigh the benefits for most patients.

Generalized Pain Disorders

Patients with generalized, whole-body pain are often referred for evaluation of possible neuropathy but rarely have a neurologic disorder. The conditions that result in generalized body pain are usually psychiatric or rheumatologic in origin. Psychiatric conditions that may produce whole-body pain include depression, anxiety, malingering, adjustment disorders, and conversion disorders. The difficult task in treating these patients is to help them recognize the psychiatric component of their illness, not feel insulted by the diagnosis, and facilitate contact with a psychiatrist who will be better suited to treat their problems.

Fibromyalgia

Although not a neurologic disease, many patients with fibromyalgia are evaluated by neurologists. This disease of uncertain etiology affects mostly younger and middle-aged women and is characterized by aching pain involving the neck,

mid-back, lower back, arms, legs, and chest wall. Patients with fibromyalgia may also describe burning, tingling, and lancinating pains. Weakness is a subjective complaint, although none is demonstrable on examination. Neurocognitive symptoms include forgetfulness, impaired concentration, and fatigue. Research diagnostic criteria include the presence of chronic widespread pain and tenderness to palpation of 11 of 18 specific points [16]. By the time a patient with fibromyalgia is referred to a neurologist, an extensive battery of tests to exclude other diagnoses is usually available for interpretation. False-positive results are common due to the sheer number of studies ordered. Treatment of fibromyalgia is frequently challenging. A straightforward discussion of the diagnosis reduces accumulation of disability, whereas evasiveness and unnecessary, protracted evaluations do more harm than good [17]. Patients with fibromyalgia may show a modest response to antidepressants. Nonsteroidal anti-inflammatory drugs are usually not effective, and narcotics should be avoided. Encourage patients to pursue alternative therapies, as conventional medical treatment is frequently disappointing. In some cases, referral to a rheumatologist (preferably one with an interest in the condition who will not dismiss the patient) may be helpful.

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Focal Pain Syndromes of the Extremities

16

Introduction

It is easy to assume that all patients referred to a neurologist for the evaluation of limb pain have neurological problems such as radiculopathies, compression neuropathies, or plexopathies and that more common musculoskeletal problems have been excluded prior to referral. In practice, this is far from true, and a neurologist, therefore, must have a thorough grasp of both the neurologic and non-neurologic causes of pain and the modalities available for their treatment. This chapter is organized into three sections:

- Common neurologic sources of limb pain and the musculoskeletal conditions which most commonly mimic them (Table 16.1). Briefly, neurologic causes of pain are more likely when there is weakness, objective sensory loss, and paresthesias, whereas musculoskeletal conditions are more likely if there is a limitation in the range of motion, tenderness to palpation, and pain that has an aching quality.
- Treatment of nociceptive pain. The treatment of pain secondary to neurologic and musculoskeletal disorders differs considerably: while neurologic sources of pain respond to medications for neuropathic pain (Chap. 15), musculoskeletal disorders need medications for nociceptive pain and are more likely to require surgical intervention.
- Controversial localized pain syndromes. Complex regional pain syndrome and myofascial pain syndrome occupy the borderlands of neurology, psychiatry, and rheumatology and pose management challenges that require familiarity with all three fields.

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Table 16.1 Common neurologic and musculoskeletal causes of limb pain

Location	Neurologic conditions	Musculoskeletal conditions
Shoulder and proximal arm	C5 radiculopathy upper trunk brachial plexopathy	Rotator cuff tendonitis
Lateral forearm	C6 radiculopathy	Lateral epicondylitis (tennis elbow)
Medial hand and forearm	Ulnar neuropathy C8 radiculopathy lower trunk brachial plexopathy	Medial epicondylitis (golf elbow)
Lateral hand including thumb	Carpal tunnel syndrome	de Quervain's tenosynovitis carpometacarpal joint arthritis
Hip and proximal leg	L2–3 radiculopathy meralgia paresthetica lumbosacral plexopathy	Osteoarthritis of the hip trochanteric bursitis
Knee	L3 radiculopathy gonalgia paresthetica	Osteoarthritis of the knee
Foot (Chap. 15)	polyneuropathy tarsal tunnel syndrome	Plantar fasciitis

Shoulder and Proximal Arm Pain

C5 Radiculopathy

C5 radiculopathy is characterized by neck pain and paresthesias that radiate into the shoulder and upper arm. On occasion, arm pain may be present without any neck pain. Weakness of deltoid, biceps, and infraspinatus may occur but is usually less prominent than the sensory complaints.

Brachial Plexopathy

Only a small percentage of patients referred to a neurologist for the question of brachial plexopathy will have a plexus lesion. The three most important etiologies of brachial plexopathy are trauma, cancer, and idiopathic brachial neuritis, each of which has a distinctive presentation.

Trauma

Trauma may affect the brachial plexus at any level. The best-known traumatic plexopathy is Erb's palsy, caused by damage to the upper trunk of the plexus, usually from downward pressure on the shoulder with forceful separation of the shoulder from the head. In addition to pain, there is weakness of deltoid, biceps, supraspinatus, and infraspinatus. Sensation is decreased over the lateral upper arm and sometimes the lateral forearm. EMG should be performed no sooner than 3 weeks after suspected trauma to provide the most accurate information

concerning localization and prognosis. In many cases, it is necessary to image the brachial plexus and cervical spine to differentiate traumatic brachial plexopathy from cervical polyradiculopathy. This is especially true for severe injuries which may produce nerve root avulsion.

Cancer

Neoplastic infiltration of the brachial plexus results in exquisite pain in the suprascapular and supraclavicular regions that radiates into the shoulder and arm and persists or is worse at night. Weakness and wasting of the arm and hand muscles follow the pain by several weeks or even months. Horner syndrome may develop. The most common cancers that infiltrate the brachial plexus are breast and lung carcinomas. Unfortunately, patients with infiltrative brachial plexopathies have a poor prognosis and usually do not survive long enough to make a neurologic recovery. Local radiation, narcotic analgesics, and agents for neuropathic pain are used to palliate symptoms.

Radiation-induced brachial plexopathy develops months to years after local radiotherapy for breast or lung cancer. The challenge in diagnosing radiation-induced plexopathy is to differentiate it from direct infiltration by tumor recurrence. Clinically, radiation-induced plexopathy is more likely to be painless than infiltrative plexopathy is. Electrophysiologically, radiation-induced plexopathy is more likely when myokymia is found. MRI of the brachial plexus helps to differentiate between the two conditions: nodular enhancement and mass lesions suggest neoplastic infiltration [1]. Because radiation-induced plexopathy is secondary to ischemic damage and fibrosis, it is frequently refractory to all treatments.

Idiopathic Brachial Neuritis

Idiopathic brachial neuritis (also known as brachial plexitis or Parsonage-Turner syndrome) has a characteristic presentation of intense local neck or shoulder pain followed several days to weeks later by arm weakness. Most patients report a viral prodrome or vaccination several weeks before the plexopathy develops. The mainstay of treatment of idiopathic brachial neuritis is pain control with agents for neuropathic symptoms. In some cases, the pain is so severe that narcotics are required. Steroids are often prescribed, though their exact benefit is unclear. Idiopathic brachial neuritis is a self-limited condition that usually improves after several months. In some cases, however, the improvement is minimal, and patients are left with extreme disability.

Rotator Cuff Tendonitis

Inflammation of the tendons of the rotator cuff causes pain localized to the lateral shoulder that is reproduced by repetitive overhead reaching or by lying on the affected side. On examination, patients have point tenderness over the lateral acromion, supraspinatus or infraspinatus tendons, and pain with passive abduction at the shoulder. The weakness perceived by the patient and often found on examination is

due to guarding, tendon instability, and disuse atrophy, rather than to true neurologic dysfunction. The cornerstones of treatment include ice, NSAIDs, and avoidance of activities that exacerbate the pain. For patients who do not respond to conservative measures, local steroid injections are helpful. Surgery is reserved for patients with refractory pain or rotator cuff tears.

Lateral Arm Pain

C6 Radiculopathy

C6 radiculopathy is characterized by pain and paresthesias that radiate from the neck into the lateral arm and hand, including the thumb. There may be weakness of biceps, triceps, and wrist flexors.

Lateral Epicondylitis

Lateral epicondylitis is produced by inflammation of the extensor carpi radialis longus and brevis tendons. Pain secondary to lateral epicondylitis is elicited by palpating the painful area, while the patient resists wrist extension. Treatment includes rest, ice, and NSAIDs, with corticosteroid injections reserved for patients with refractory symptoms.

Medial Hand and Arm Pain

Ulnar Neuropathy

The most common symptoms of ulnar neuropathy are paresthesias and numbness in the palmar surface of the fifth and medial half of the fourth digits. Ulnar neuropathy is most often the result of repetitive microtrauma to the nerve as it passes around the elbow. Precipitants include resting the elbows on a table or lying flat on the back, while the arms are supinated. On examination, weakness involves finger abduction and flexion of the distal interphalangeal joints of digits four and five. There may be atrophy of the hypothenar eminence and first dorsal interosseous. Sensory loss is found over both the palmar and dorsal surfaces of the fifth and medial half of the fourth digits and palm (Fig. 16.1). Severe ulnar neuropathy produces a claw hand in which hyperextension at the fourth and fifth metacarpophalangeal joints is accompanied by flexion of the interphalangeal joints. A Tinel sign is present at the elbow when paresthesias occur upon percussing the ulnar nerve as it runs between the olecranon process and medial epicondyle. Ulnar neuropathy may be confirmed by nerve conduction studies. Conservative treatment includes avoiding precipitating activities and wearing a padded elbow sleeve to prevent further microtrauma to the

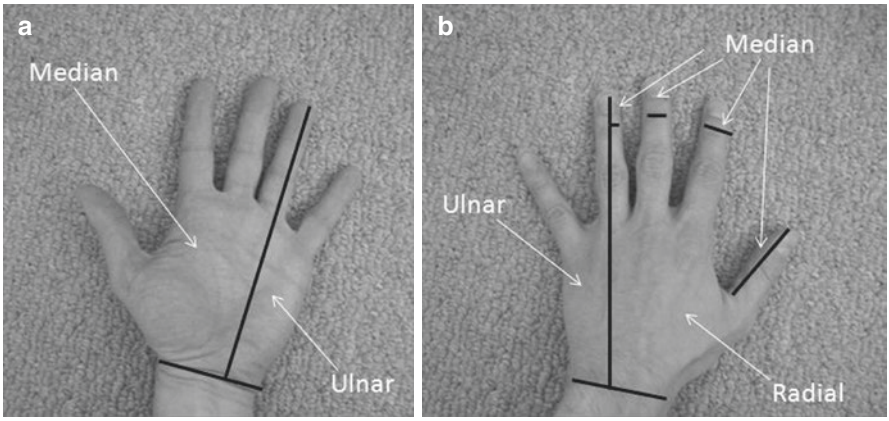

Fig. 16.1 The sensory innervation of the hand. (**a**) palmar surface, (**b**) dorsal surface

nerve. Consider surgical decompression and nerve transposition should conservative measures fail.

C8 Radiculopathy

Expected complaints of C8 radiculopathy are neck pain and paresthesias radiating into the medial hand and forearm. Numbness in this distribution may accompany weakness of the intrinsic muscles of the hand. Because structural radiculopathies at the C8 levels are relatively uncommon, carefully consider more common possibilities such as ulnar neuropathy at the elbow before making the diagnosis.

Lower Trunk Brachial Plexopathy

The lower trunk of the brachial plexus is comprised of nerve fibers derived from the C8-T1 roots, and damage at this site may cause pain and other sensory complaints in the medial hand, forearm, and arm. The lower trunk of the plexus, like the upper trunk, may be damaged by trauma, cancer, or idiopathic inflammatory conditions. A Horner syndrome may accompany a lower trunk plexopathy because the lower trunk lies in proximity to the oculosympathetic chain (Chap. 7). One cause of lower trunk brachial plexopathy deserves special mention because of its rarity: thoracic outlet syndrome. True neurogenic thoracic outlet syndrome is caused by compression of the lower trunk of the brachial plexus by a cervical rib or accessory band of connective tissue [2]. It requires rigorous investigation including electromyography and thoracic imaging to confirm the presence of a responsible structural abnormality. In most cases, the diagnosis of thoracic outlet syndrome is incorrect and is applied to patients with arm pain of unclear etiology.

Medial Epicondylitis

Medial epicondylitis (golf elbow) is produced by inflammation of the flexor carpi radialis tendon, usually resulting from repetitive gripping movements and wrist flexion. Pain is localized to the medial elbow, and because of the well-known course of the ulnar nerve around the elbow, patients with medial epicondylitis are often referred to neurologists for evaluation of ulnar neuropathy. Pain secondary to medial epicondylitis is elicited by palpating the painful area while, the patient resists wrist flexion. Imaging studies should be obtained only to exclude alternative diagnoses. Treatment for medial epicondylitis involves rest, ice, and NSAIDs. Corticosteroid injections and gradual introduction of grip-strengthening exercises may also help.

Lateral Hand Pain

Carpal Tunnel Syndrome (CTS)

Compression of the median nerve at the wrist results in CTS. In the early stages of the disorder, patients describe pain and paresthesias in the hand, mostly in the first three digits and the radial half of the fourth digit. It is also common for patients to report symptoms in the entire hand or extending proximally into the forearm and upper arm, even though these areas are outside of the sensory distribution of the median nerve. Hand overuse, particularly typing, mouse use, and assembly work, precipitate or exacerbate the symptoms. Nocturnal symptoms are common, and patients may shake out their hands to relieve the paresthesias. Motor problems are not prominent early in CTS, but as the disorder progresses, the hand and fingers may become weak, and grip strength may be reduced. On examination, look for weakness of thumb abduction and flattening of the thenar eminence. The sensory loss in CTS affects the palmar surfaces of the first three digits and the lateral half of the fourth digit (Fig. 16.1). Because the palmar sensory branch does not pass through the carpal tunnel, sensation over the palm should be spared. The Tinel and Phalen signs support the diagnosis. Tinel sign (Fig. 16.2) is present when tapping the volar aspect of the wrist briskly with a reflex hammer produces paresthesias in the first three fingers. Phalen sign (Fig. 16.3) is present when 1 minute of wrist flexion with the dorsal hands opposed to each other produces paresthesias in the palmar surfaces of the first three fingers. Physical examination abnormalities may be limited in early CTS, and nerve conduction studies may be necessary to make the diagnosis. Patients with mild disease may improve with wrist braces and activity restriction. Local corticosteroid injections are a temporizing measure which may reduce sensory symptoms. Carpal tunnel release surgery is the definitive treatment for patients with more severe CTS.

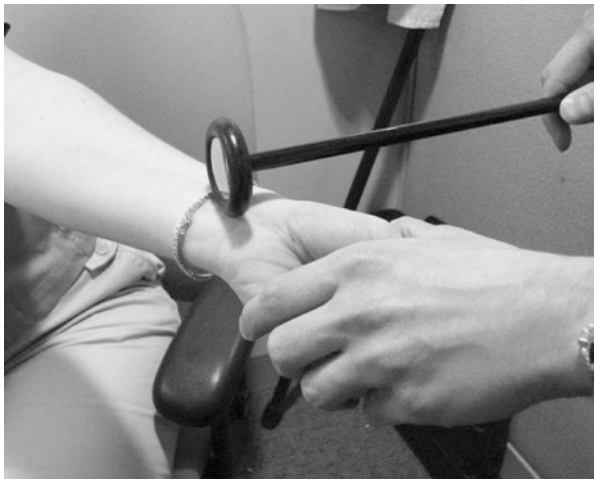

Fig. 16.2 Tinel sign. Tap the distal volar aspect of the wrist briskly with a reflex hammer. The sign is positive when the patient reports paresthesias in the palmar surfaces of digits 1–3

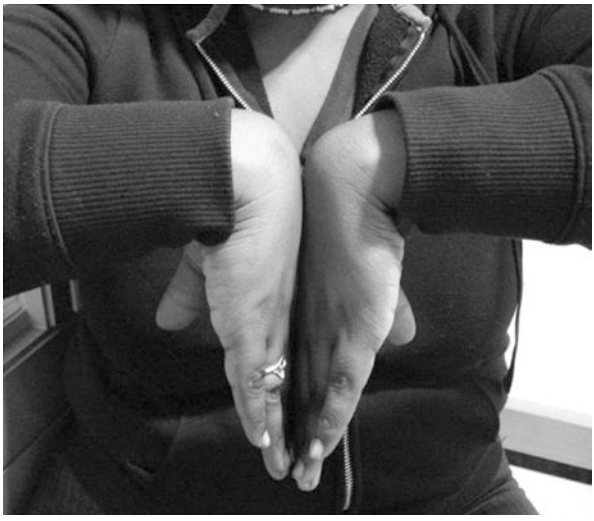

Fig. 16.3 Phalen sign. Instruct the patient to oppose the dorsal surfaces of the hands for 1 minute. Patients with carpal tunnel syndrome will report paresthesias in the palmar surfaces of digits 1–3

De Quervain's Tenosynovitis

This condition, caused by inflammation of the tendons of the extensor pollicis brevis and abductor pollicis longus, may lead to referral for carpal tunnel syndrome or superficial radial neuropathy. Patients with de Quervain tenosynovitis describe pain in the thumb and radial styloid, especially with pinching maneuvers. On examination, the radial styloid and adjacent wrist are tender to palpation. The Finkelstein test is a provocative maneuver for de Quervain tenosynovitis in which pain is reproduced by enclosing the thumb inside the fist and deviating the wrist in the ulnar direction (Fig. 16.4). Treat de Quervain tenosynovitis with rest, NSAIDs, and

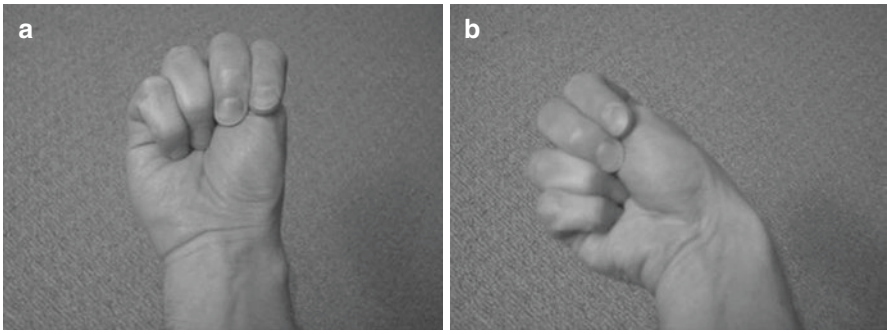

Fig. 16.4 The Finkelstein maneuver. Instruct the patient to enclose his thumb inside their fingers (3A) and deviate the hand in the ulnar direction (3B). Patients with de Quervain tenosynovitis will note pain in the lateral aspect of the thumb

immobilization of the thumb using a thumb spica splint. Refractory cases may require corticosteroid injection and possibly surgical referral.

Carpometacarpal (CMC) Joint Arthritis

Osteoarthritis of the CMC joint is present in the majority of people over 65. It is characterized by pain at the base of the thumb and radial aspect of the wrist and sometimes by grip weakness. This condition often leads to neurological consultation for evaluation of carpal tunnel syndrome. The diagnosis of CMC joint arthritis is established by finding tenderness to compression at the carpometacarpal joint (Fig. 16.5). Plain radiographs, though usually not necessary, confirm the diagnosis. Treatment involves immobilization, NSAIDs, and heat application.

Thigh and Hip Pain

L2 and L3 Radiculopathy

While intervertebral disc herniations usually do not affect the upper lumbar nerve roots, spinal stenosis is a common cause of upper lumbar radiculopathy in older patients. Pain and paresthesias may radiate from the back into the lateral (L2) or medial thigh (L3). Weakness of hip flexion, hip adduction, and knee extension may accompany an upper lumbar radiculopathy. The patellar reflex may be reduced or absent. Because it may be challenging to differentiate among upper lumbar radiculopathy, lumbosacral plexopathy, and femoral neuropathy by history and physical examination, nerve conduction studies and electromyography are often required.

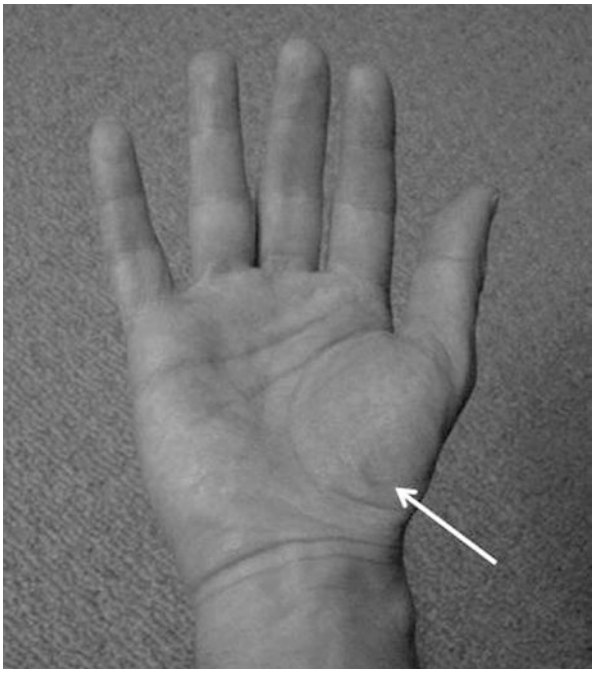

Fig. 16.5 The carpometacarpal joint

Meralgia Paresthetica

Entrapment of the lateral femoral cutaneous nerve, usually at the inguinal ligament, leads to meralgia paresthetica. Pain and paresthesias, often quite severe, involve the lateral thigh and sometimes radiate into the knee. Because this nerve has no motor distribution, there is no muscle weakness: any muscle weakness on examination is due to guarding or to an unrelated condition. Meralgia paresthetica usually develops in patients who are obese, who have lost a large amount of weight, or who wear tight clothes, particularly heavy tool belts. Pregnant women are also susceptible. Nerve conduction studies are frequently unhelpful in establishing the diagnosis, as a sensory response from the lateral femoral cutaneous nerve is difficult to obtain, even in normal subjects. Meralgia paresthetica may improve with weight loss and avoidance of restrictive clothing. Most patients, however, do not improve with these conservative measures and require local steroid injections at the inguinal ligament [3]. Surgery is required only on rare occasions.

Lumbosacral Plexopathy

Many of the general rules for brachial plexopathy also apply to lumbosacral plexopathy. Although etiologies common to both brachial and lumbosacral plexopathies

include trauma, cancer, and idiopathic lumbosacral plexitis, there are several distinct pathologies that affect the lumbosacral plexus.

Trauma

Traumatic lumbosacral plexopathy results from severe pelvic trauma (usually sufficiently severe to cause a fracture) or pelvic surgery. Depending on the site of trauma, sensorimotor symptoms may involve the entire leg or just a restricted part of it. EMG helps to localize and quantify the deficits. Lumbosacral plexopathy related to pregnancy is a specific traumatic etiology which is discussed further in Chap. 11.

Retroperitoneal Hematoma

Retroperitoneal hematoma, usually secondary to anticoagulation, a bleeding diathesis, or procedure involving femoral catheterization, is an important cause of lumbosacral plexopathy. Rapid identification of the problem and correction of any contributing coagulation abnormalities may prevent life-threatening exsanguination. Plexopathy related to hematoma tends to resolve as the blood is reabsorbed.

Cancer

Neoplasm-related lumbosacral plexopathies, like those that involve the upper extremity, may be divided into infiltrative and radiation-induced plexopathies, and are evaluated similarly. The most common tumors that infiltrate the lumbosacral plexus are colon and ovarian cancers.

Diabetic Amyotrophy (Diabetic Lumbosacral Radiculoplexus Neuropathy)

Most patients who develop this disorder of the lumbosacral nerve roots and plexus have mild type 2 diabetes. Weight loss, fevers, and night sweats frequently precede or accompany the syndrome. Diabetic amyotrophy begins with exquisite pain, usually in the hip and thigh, which often spreads to involve the lower leg and, in many cases, the contralateral leg. Leg weakness, often profound, develops several days later. Patients with diabetic amyotrophy require pain control with agents for neuropathic pain and sometimes with narcotics. Physical therapy may help restore mobility. The role of immunomodulatory therapy including intravenous methylprednisolone and IVIg in diabetic amyotrophy is controversial [4]. Unfortunately, recovery may take many months to years and is often incomplete.

Idiopathic Lumbosacral Plexitis

Idiopathic lumbosacral plexitis, though similarly named, should not be considered the lower extremity counterpart of idiopathic brachial neuritis, as it is generally a more severe disorder. Idiopathic lumbosacral plexitis is essentially the same condition as diabetic amyotrophy, except that diabetes is not identified as a contributor [5].

Trochanteric Bursitis

Trochanteric bursitis is caused by breakdown of the bursa surrounding the greater trochanter of the femur. It often accompanies or is confused with meralgia

paresthetica or upper lumbar radiculopathy. Pain is localized to the lateral hip and becomes worse when the patient moves the hip or lies on it. Trochanteric bursitis is diagnosed clinically by finding tenderness to palpation of the trochanteric bursa. Conservative treatment includes a combination of NSAIDs, heat, and physical therapy. Local steroid injections may benefit patients who do not respond to these measures.

Osteoarthritis of the Hip and Occult Hip Fracture

Osteoarthritis, almost universal in the elderly population, is a common cause of hip pain. Because pain may radiate into the groin, back, or knee, hip osteoarthritis may lead to evaluation for lumbosacral radiculopathy. Patients typically report groin pain with attempted internal rotation of the hip. Treatment with NSAIDs may help, but patients often require orthopedic referral. Severe anterior or lateral hip pain with difficulty bearing weight suggests the possibility of hip fracture and should prompt plain films of the hip and orthopedic referral.

Knee Pain

Isolated knee pain results so rarely from a neurologic process that more common orthopedic conditions should be evaluated exhaustively before undertaking any neurologic investigation. L3 radiculopathy is a possible source of knee pain but is almost always accompanied by back pain that radiates into the leg. Gonalgia paresthetica is an even less common cause of knee pain that results from entrapment of the infrapatellar branch of the saphenous nerve.

General Principles of Nociceptive Pain Treatment

In the ideal world, neurologists would treat pain exclusively of neuropathic origin. The musculoskeletal pain syndromes described in this chapter produce nociceptive rather than neuropathic pain and require a treatment strategy outside of the realm of traditional neurologic interventions. The standard approach to nociceptive pain management involves escalating from weaker doses of medications with few side effects, to stronger medications that may have more side effects, to multidisciplinary pain treatment, to alternative therapies:

- Although most nociceptive pain responds to over-the-counter medications such as acetaminophen, aspirin, ibuprofen, and naproxen, patients who respond to one of these treatments usually do not come to neurological attention.
- Prescription nonsteroidal anti-inflammatory drugs (NSAIDs) are effective for some patients who do not respond to over-the-counter analgesics. Common prescription-strength NSAIDs include ketorolac (10 mg qid for up to five consecutive days), diclofenac (100 mg bid), and meloxicam (15 mg qd). Side effects of these medications include gastrointestinal hemorrhage and nephrotoxicity.

- Physical therapy, ice, heat, and massage are effective for some patients with musculoskeletal pain.
- The opioid agonist/serotonin-norepinephrine reuptake inhibitor tramadol (50–100 mg bid) has a lower rate of side effects than narcotic medications and may be used to treat a variety of musculoskeletal complaints refractory to acetaminophen or NSAIDs.
- Narcotic analgesics should be avoided if possible, as these medications have addictive properties, are sedating, and have a thriving black market for resale. Avoid fast-onset, short-acting narcotics such as hydrocodone, oxycodone, hydromorphone, meperidine, and short-acting morphine, as their brief durations of action lead to frequent spikes in pain and high potential for abuse. Longer-acting narcotic options include fentanyl patches or methadone, both of which should still be prescribed sparingly.
- Local anesthetic or steroid injections may be helpful for patients with a multitude of musculoskeletal conditions that do not respond to oral medications.
- Many pain syndromes are difficult to treat due to the severity of the underlying condition or to superimposed or preexisting psychological factors. Tricyclic antidepressants, selective serotonin reuptake inhibitors, and anticonvulsants may help patients with refractory chronic pain and comorbid psychiatric disease.
- Psychological counseling, biofeedback, and alternative treatments such as acupuncture and homeopathic treatments may be effective for severe pain.

Controversial Localized Pain Syndromes

Complex Regional Pain Syndrome (CRPS)

This disorder, alternatively known as reflex sympathetic dystrophy or causalgia, is characterized by pain, edema, trophic skin changes, and decreased range of motion in an extremity. In the early stages, however, pain may be unaccompanied by other signs and symptoms. Patients are divided into CRPS type I in which there is no definable nerve lesion and CRPS type II in which there is a history of a preceding nerve injury. The mechanism by which CRPS develops is unclear, and the diagnosis is a controversial one. Many patients with limb pain of uncertain etiology are told that they have CRPS when no clear source for their pain can be identified.

Myofascial Pain Syndrome

Myofascial pain syndrome is the name that is often assigned to any focal musculoskeletal pain of unclear etiology despite thorough investigation. Problems such as depression, fatigue, and forgetfulness frequently accompany the pain. Myofascial pain syndrome may represent a restricted form of fibromyalgia and responds (or fails to respond) to the same treatments as that disorder (Chap. 15).

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Back Pain, Myelopathy, and Radiculopathy

17

Definitions, History, and Examination

Although back and neck pain are commonly managed by primary care physicians, they may come to neurological attention when they are refractory to treatment or when they are accompanied by signs or symptoms of radiculopathy, myelopathy, or cauda equina syndrome.

Radiculopathy

Radiculopathy is the clinical syndrome caused by damage to a nerve root or more properly the mixed spinal nerve containing both sensory and motor fibers. The classic history for radiculopathy is back or neck pain that radiates into the arm or leg in a band-like distribution. The pain should have a sharp, burning, or stabbing character and is often accompanied by paresthesias. Although a monoradiculopathy may produce weakness, this is often mild because most muscles are innervated by more than one nerve root (Table 17.1). Sensory loss due to radiculopathy follows a dermatomal distribution and may be mild or incomplete due to the overlapping distributions of the cutaneous sensory nerves (Table 17.2 and Chap. 15, Fig. 15.1). Patients with radiculopathy may have focal weakness (Chap. 11) or sensory disturbances (Chap. 16) in the extremities without accompanying back pain. The two most useful provocative tests for radiculopathy are the straight leg raise test for lumbosacral root lesions and the Spurling test for cervical root lesions. To perform the straight leg raise test, instruct the patient to lie supine with the leg extended. Leg pain with passive flexion of the hip between 30° and 70° suggests the presence of a herniated disc secondary to L5 or S1 root compression. Anterior thigh pain with passive extension of the hip while the patient is prone suggests L2 or L3 root compression. To perform a Spurling test, instruct the patient to tip their head to the symptomatic side and press from above; the test is positive if compressing the head causes pain and paresthesias to radiate into the symptomatic arm.

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Table 17.1 Muscle weakness organized by myotomes

Root level	Weak muscles
C5 + C6	Deltoid, biceps, supraspinatus, infraspinatus
C6 + C7	Triceps, wrist extensors, wrist flexors
C8 + T1	Abductor pollicis brevis, abductor digiti minimi, extensor indicis proprius
L2 + L3	Iliopsoas, adductor longus, quadriceps
L4	Tibialis anterior, quadriceps
L5	Tibialis anterior, tibialis posterior, peroneus longus, gluteus medius
S1	Gastrocnemius, hamstrings, gluteus maximus

See Chap. 10 for additional details of testing

Table 17.2 Sensory loss organized by dermatomes

Root level	Distribution of sensory symptoms
C5	Lateral upper arm
C6	Lateral forearm, thumb, and index finger
C7	Midline of forearm, middle finger
C8	Medial forearm, ring, and pinky finger
T1	Medial upper arm
L2	Lateral thigh
L3	Medial thigh
L4	Medial leg
L5	Lateral leg and dorsum of foot
S1	Lateral foot, sole, and Achilles tendon
Lower sacral roots	Perineum, scrotum

See also Chap. 15, Fig. 15.1

Myelopathy

Myelopathy is the pattern of sensorimotor deficits produced by damage to the spinal cord. An understanding of spinal cord neuroanatomy is necessary to determine the spinal cord level that is producing myelopathic deficits. For the purposes of clinical localization, the spinal cord consists of (Fig. 17.1):

- The dorsal columns which contain ascending sensory fibers mediating vibration and proprioception. Dorsal column lesions produce sensory deficits below the level of the lesion on the same side of the body.
- The lateral spinothalamic tracts which contain ascending sensory fibers mediating pain and temperature. Spinothalamic tract lesions produce sensory deficits in all dermatomes beginning one to two levels below the level of the lesion on the opposite side of the body.
- The lateral corticospinal tracts which contain descending motor fibers. Corticospinal tract lesions produce weakness and spasticity below the level of the lesion on the same side of the body.
- The dorsal horns which relay all sensory information from the dorsal root ganglia to the dorsal columns and lateral spinothalamic tracts. Dorsal horn lesions

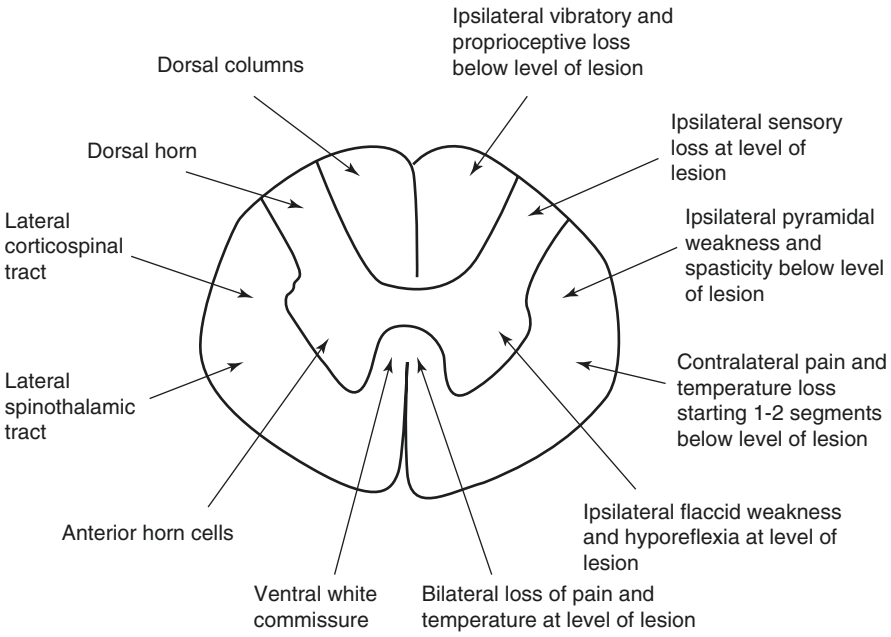

Fig. 17.1 Cross-sectional diagram of the spinal cord showing locations of the clinically important structures on the left and expected clinical deficits on the right

produce loss of all sensory modalities at the level of the lesion on the same side of the body.

- The anterior horns which contain the lower motor neurons. Anterior horn cell lesions produce flaccid paralysis at the level of the lesion on the same side of the body.
- The ventral white commissure which contains decussating sensory fibers connecting the pain and temperature information in the dorsal horns to the contralateral spinothalamic tracts. Commissural lesions produce sensory loss one or two levels below the lesion both ipsilaterally and contralaterally.

A complete myelopathy, therefore, produces sensorimotor loss at myotomes and dermatomes caudal to the level of the lesion, hyperreflexia, and upgoing toes. In addition, cord lesions lead to urgency of both bowel and bladder.

In the acute stage of a severe spinal cord lesion, the limb will be flaccid and will not become spastic for several days to a few weeks following the injury. While severe lesions may produce complete plegia of the limbs, milder paresis with disproportionately greater weakness of the "upper motor neuron" muscles (see Chap. 10, Table 10.1) is more common. Be aware, though, that upper motor neuron weakness is a general guideline rather than a hard and fast rule and that many patients with spinal cord lesions do not have weakness that strictly conforms to this pattern.

Cauda Equina Syndrome

The lumbar and sacral nerve roots emerge from the spinal column to form the cauda equina. Compression or infiltration of the cauda equina produces a distinctive lumbosacral polyradiculopathy characterized by weakness and sensory loss in the lower extremities, sphincter weakness with incontinence of both bowel and bladder, and sensory loss in the perineum. Examination clues to cauda equina syndrome are reduced sphincter tone and absent anal wink. Anal sphincter tone is established by placing the finger inside the anus and asking the patient to bear down. An anal wink is tested by stroking the perianal skin and observing for contraction of the anal sphincter. Cauda equina syndrome is a true neurologic emergency and should be evaluated and treated as quickly as possible. In most cases, it is secondary to a large, posterior lumbar disc herniation and requires urgent surgical decompression. Important inflammatory causes of cauda equina syndrome include neoplastic invasion and cytomegalovirus infection.

Compressive Myelopathies and Radiculopathies

Red Flags

When evaluating back and neck pain, it is critical to seek red flags that point to dangerous conditions such as malignancy, epidural abscess, cord compression, or cauda equina syndrome. Any patient with a history of cancer, fevers, bowel or bladder dysfunction, or rapidly progressive weakness requires urgent imaging of the clinically involved area of the spine, preferably MRI with and without contrast. Also consider urgent MRI for patients with thoracic-level signs or symptoms, as malignant processes such as epidural cord compression and epidural abscess have a propensity to involve this section of the spine. CT does not offer the same image resolution as MRI does but may provide some helpful information in patients who cannot undergo MRI.

Herniated Nucleus Pulposus

The intervertebral discs lie between the vertebral bodies, provide the spine with structural stability, and allow joint mobility. The discs consist of a tough fibrous annulus fibrosus surrounding a softer, more gelatinous nucleus pulposus. Herniation of the nucleus pulposus is the most common cause of radiculopathy and myelopathy in people between the ages of 30 and 50. Trauma or excessive stretching or exercise may precede symptoms immediately, but clear precipitants of intervertebral disc herniation are often absent. Although the precise mechanisms by which disc herniations produce symptoms are not entirely clear, it is likely that the herniated disc incites an inflammatory reaction leading to pain, while physical compression of the nerve root within the neural foramen or the spinal cord within the central canal is mechanistically more important in generating weakness and sensory loss. Disc

Table 17.3 Common intervertebral disc herniation syndromes

Direction of herniation	Herniation at C5–6	Herniation at C6–7	Herniation at L4–5	Herniation at L5–S1
Posterior	Spinal cord	Spinal cord	L5 nerve root, possibly cauda equina	S1 nerve root, possibly cauda equina
Posterolateral	C6 nerve root	C7 nerve root	L5 nerve root	S1 nerve root
Far lateral	C6 nerve root	C7 nerve root	L4 nerve root	L5 nerve root

herniations are most common at the C5–6, C6–7, L4–5, and L5–S1 levels and are distinctly uncommon in the thoracic spine. Discs may herniate posteriorly, posterolaterally, or far laterally, compressing different structures in each case. Table 17.3 summarizes the deficits expected with disc herniation at each of the four most common spinal levels.

If there are no red flags, treat patients with suspected herniated intervertebral discs conservatively and defer neuroimaging studies. Because resuming normal activity should be the goal of patients with intervertebral disc herniation, I usually recommend that patients continue their normal routines rather than beginning programs of bed rest or aggressive "boot camp" physical therapy. Instruct patients with cervical disc disease to wear a soft cervical collar at night while using a computer and while driving. Prescribe mild pain relievers including ibuprofen and acetaminophen as the first line of analgesia. Stronger medications including tramadol (50–100 mg bid) and long-acting narcotics (sustained release oxycodone 10–20 mg bid, used sparingly) may be prescribed cautiously for patients with severe symptoms. Because back pain is often chronic, it is best to avoid narcotic medications as much as possible. A short trial of corticosteroids (e.g., prednisone 60 mg × 3 days, 40 mg × 3 days, 20 mg × 3 days) is sometimes helpful in reducing the inflammation produced by a herniated disc. Agents for neuropathic pain such as gabapentin, pregabalin, and nortriptyline are usually not effective for patients with disc herniation but may be considered in patients with refractory pain.

If conservative therapy does not improve symptoms after 6 weeks, more aggressive evaluation and treatment are indicated. MRI of the clinically involved level of the spine should be used to confirm the diagnosis and possibly to plan surgery. Electromyography may be considered but rarely offers any additional helpful information. Epidural steroid injections may provide short-term relief of pain but lack long-term efficacy and do little to nothing for motor deficits [1, 2]. Surgical referral is indicated for patients with pain that persists despite 6 weeks of conservative therapy, progressive motor deficits, or incontinence of bowel or bladder.

Spinal Stenosis

As people age, the intervertebral discs desiccate, and a greater portion of the axial load must be assumed by the facet joints and ligamentum flavum. The combination of disc herniation, facet joint and ligamentous hypertrophy, and bony spur

formation leads to osteoarthritic narrowing of the central spinal canal and neural foramina (Fig. 17.2). Like intervertebral disc herniation, spinal stenosis may produce back pain, radiculopathy, myelopathy, or a cauda equina syndrome. Unlike symptoms from disc herniation, those from spinal stenosis typically develop in a subacute to chronic fashion. Spinal stenosis may also be distinguished from disc herniation by its greater tendency to involve the upper lumbar levels.

A unique manifestation of spinal stenosis is neurogenic claudication characterized by pain and fatigue in the back and legs that develops with standing or walking and is relieved by rest and bending forwards. Neurogenic claudication can be distinguished from vascular claudication of the lower extremities on clinical grounds (Table 17.4). In many older patients, neurogenic and vascular claudication coexist. If there is any doubt as to the source of claudication symptoms, referral to a vascular specialist may help to reach the correct diagnosis.

Abnormal neuroimaging findings in patients with spinal stenosis must be interpreted cautiously, as many asymptomatic older people have radiographic evidence

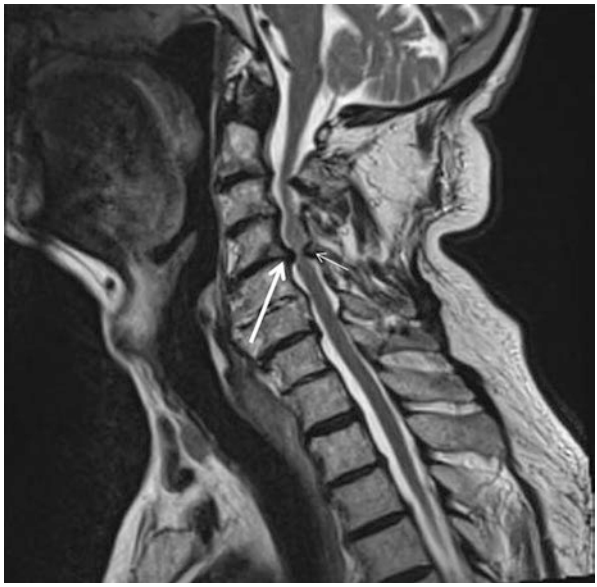

Fig. 17.2 Sagittal T2-weighted MRI shows herniated intervertebral disc (thick arrow) and hypertrophic ligamentum flavum (thin arrow) in a patient with spinal stenosis. Note the disappearance of the hyperintense CSF signal at the greatest level of stenosis. The faint hyperintense signal change in the spinal cord indicates cord compression

Table 17.4 Differentiating between neurogenic and vascular claudication

Clinical feature	Neurogenic claudication	Vascular claudication
Pain improves with flexion (e.g., leaning over a shopping cart)	Yes	No
Pain relief after rest	After several minutes	Almost immediately
Peripheral pulses	Normal	Reduced
Leg weakness	May be present	Should be absent

of degenerative arthritis. Electromyography is unhelpful in diagnosing spinal stenosis or in planning its treatment. Conservative therapy of spinal stenosis is similar to that described for intervertebral disc herniation. Unfortunately, most patients with spinal stenosis do not improve markedly with physical therapy, medications, or epidural steroid injections. Consider surgery for patients with intractable pain, sphincter dysfunction, progressive weakness, or disabling exercise intolerance. Many spine surgeons are understandably reluctant to perform operations for older patients with spinal stenosis, as these patients frequently require multilevel operations, have medical comorbidities that make them poor surgical risks, and improve modestly at best with surgery.

Neoplasm

Neoplastic epidural cord compression, caused most often by metastasis, represents a neurologic emergency. The most common tumors that produce cord compression are those of the breast, lung, prostate, and lymphoreticular system [3]. Primary tumors including ependymoma, astrocytoma, meningioma, and chordoma are much less common causes of cord compression. The most common site of epidural cord compression is the thoracic spine, due to both its relatively rich vascular supply and to the greater number of thoracic vertebrae. Back pain, sometimes accompanied by radiculopathic symptoms is usually the first sign of metastasis, and may go unnoticed for several months, especially in patients with undiagnosed cancer. As cord compression progresses, weakness develops in a myelopathic pattern, and the patient becomes incontinent of bowel and bladder.

Any patient with known cancer who develops back pain should have an MRI with and without contrast to look for cord compression. Time is of the essence in treating epidural cord compression, as the likelihood of maintaining ambulation and continence of bowel and bladder is related to the severity of the deficits when treatment begins. Initiate corticosteroids as soon as cord compression is diagnosed: treat patients with severe weakness with 100 mg dexamethasone orally followed by 24 mg q6h, tapering the dose by 50% every 2–3 days [3]. For patients with milder symptoms, an initial bolus of 10 mg may be sufficient [4]. Definitive therapy of metastatic cord compression is determined by the patient's overall prognosis and the type of primary tumor. Treat patients who are expected to survive for at least 3 months with a combination of surgical decompression and radiotherapy [5]. Radiation without surgery is indicated for patients with radiosensitive tumors such as leukemia, lymphoma, and germ cell tumors or those with otherwise poor prognoses. In patients without a known cancer history who present with epidural cord compression, evaluate for a primary tumor with a torso CT, mammogram (for women), and testicular examination and prostate-specific antigen level (for men). If these tests do not disclose a primary neoplasm, biopsy of the lesion may aid in diagnosis. Although the overall prognosis of patients who develop metastatic cord compression is poor, the probability of maintaining ambulation is excellent if appropriate measures are taken immediately.

Epidural Abscess

Bacterial infection of the epidural space occurs by either hematogenous spread from a distant infectious source or by extension of a local infection. The most common organism responsible for epidural abscess is *Staphylococcus aureus*. Other frequently encountered organisms include *Staphylococcus epidermidis*, *Escherichia coli*, and *Pseudomonas aeruginosa*. The well-known clinical triad of back pain, fever, and neurologic deficits referable to the spine is present in a minority of patients, and the diagnosis is most often missed when the triad is incomplete. Failure to detect and treat epidural abscess leads to potentially irreversible weakness, sphincter dysfunction, and distant spread of the infection. MRI of the spine with and without contrast is the diagnostic study of choice in patients with suspected epidural abscess. Unless there are clear signs that the abscess is restricted to a specific vertebral level, the best practice is to image the entire length of the spine in order to detect all possible foci of infection. Patients with epidural abscess and neurologic dysfunction require surgical drainage plus a 6-week course of antibiotics, usually vancomycin (1 g IV bid), ceftriaxone (2 g IV bid), and metronidazole (500 mg IV q8h).

Non-compressive Myelopathies and Radiculopathies

A variety of processes, most of which are intrinsic to the spinal cord, lead to painless subacute or chronic myelopathy.

Transverse Myelitis and Multiple Sclerosis

These are two of the most common causes of myelopathy caused by intrinsic cord disease and are discussed further in Chap. 22.

Vitamin B_{12} Deficiency

Vitamin B_{12} deficiency may affect the myelin of the brain, optic nerves, spinal cord, or peripheral nerves. The most common presentation is subacute-to-chronic myelopathy with prominent numbness and paresthesia in the hands and feet. Causes of vitamin B_{12} deficiency include vegetarianism, pernicious anemia, nitrous oxide abuse, and gastric bypass. The diagnosis is straightforward when the serum B_{12} level is low. If the B_{12} level is greater than the laboratory-defined lower limit of normal but still relatively low (e.g., <500 pg/mL), look for elevated levels of methylmalonic acid to diagnose subtle B_{12} deficiency [6]. Although high-dose oral and intramuscular formulations are presumably equivalent, most patients with myelopathy

secondary to B_{12} deficiency should be treated with intramuscular B_{12}, starting at 1000 μg daily for 1 week, 1000 μg weekly for 1 month, and then 1000 μg monthly thereafter.

Spinal Cord Infarction

Spinal cord infarction is much less common than cerebral infarction. The two main varieties of spinal cord infarction are the anterior spinal artery syndrome and transverse spinal cord infarction. Both varieties tend to affect the mid-thoracic spine, as the T4–8 region is a vascular watershed territory between the upper thoracic arteries and the artery of Adamkiewicz (which enters the cord from T10-L1 and supplies the lower thoracic and lumbar regions). The typical clinical history of spinal cord infarction is sudden-onset back pain followed by weakness and sensory loss in the trunk and legs. Because the anterior spinal artery supplies the ventral 2/3 of the cord, patients with the anterior spinal artery syndrome lose motor and spinothalamic function below the level of the lesion while maintaining dorsal column sensibilities. Transverse cord infarction produces a state of spinal shock characterized by flaccid weakness, areflexia, and sphincter dysfunction. Etiologies of spinal cord stroke include emboli arising from cardiac or aortic surgery, spinal vascular malformations, and nucleus pulposus embolism. Spinal transient ischemic attacks often precede infarction in patients with arteriovenous malformations. Unfortunately, imaging of spinal cord stroke is not as reliable as is imaging of cerebral stroke. Diffusion-weighted imaging protocols for the spine are not technically reliable, and the most common MRI changes (T2 hyperintensity within the cord, with T1 images showing evidence of cord edema) are usually not visible for several days and are not specific for infarction. In some patients "owl's eyes" hyperintensities indicating infarction may be seen on axial images [7]. Occasionally, T2 hyperintensity indicating infarction of the adjacent vertebral body may be seen [8]. Treatment for spinal cord stroke is limited and focuses on supportive care, physical therapy, and modification of risk factors for vascular disease. Options for patients who have had infarcts after aortic surgery include steroids and cerebrospinal fluid drainage, though rigorous data to support either treatment is not available.

Adrenoleukodystrophy (ALD)

This X-linked disorder usually causes cognitive decline, blindness, and quadriparesis in young boys. Both men and women between their 2nd and 4th decades may develop adrenomyeloneuropathy (AMN), a milder form of the disease characterized principally by myelopathy [9]. The majority of these patients have adrenal dysfunction, and some also have cerebral involvement that predominantly involves the parietal and occipital lobes. Nerve conduction studies characteristically show slow

nerve conduction velocities reflective of demyelination. The diagnosis is established by finding elevated plasma very long chain fatty acid levels. There is no cure for ALD, but stem cell transplantation is the most effective treatment option [10].

Tropical Spastic Paraparesis

The human T-cell leukemia virus (HTLV) is endemic to the Caribbean, Japan, and Africa. It is transmitted through sexual contact, blood transfusion, or intravenous drug use. Fewer than 5% of patients infected with the virus, however, develop tropical spastic paraparesis [11]. This disorder is a slowly progressive, painless myelopathy characterized by gait instability, hyperreflexia, and sphincter dysfunction. All myelopathic patients from endemic regions or with risk factors for infection with the virus should undergo serum HTLV PCR testing. The main treatments for tropic spastic paraparesis are muscle relaxants such as baclofen and diazepam. Corticosteroids may provide some symptom relief but are not a good long-term treatment option. Diagnosis and counseling are important to prevent further transmission of the virus.

Dural Arteriovenous Fistula (AVF)

Dural AVF is an uncommon but important cause of slowly progressive, usually painless myelopathy. In general, the presentation is identical to that of other chronic myelopathies, though some patients may report that their symptoms characteristically worsen with exercise. The diagnosis is often elusive, and symptoms may progress for years before the condition is identified correctly. If dural AVF is suspected, MRI and MRA of the spine should be performed first, as these studies help to guide conventional angiography. MRI of the spinal cord shows T2 hyperintensity within the spinal cord with accompanying intradural flow voids (Fig. 17.3). Embolization of the fistula cures a minority of patients, and open surgical treatment should be considered for refractory or progressive cases [12].

Copper Deficiency Myelopathy

Copper deficiency myelopathy is characterized by slowly progressive lower extremity weakness and spasticity [13]. Patients who use excessive amounts of zinc-containing denture cream or zinc supplements are at risk for developing copper deficiency, as zinc reduces copper absorption by the gut. The diagnosis is established by finding low serum copper levels. Patients with copper deficiency also have anemia and leukopenia. Copper supplementation (at least 2 mg qd orally or intravenously) and discontinuation of any source of excess zinc may help patients with copper deficiency myelopathy, but response is usually modest.

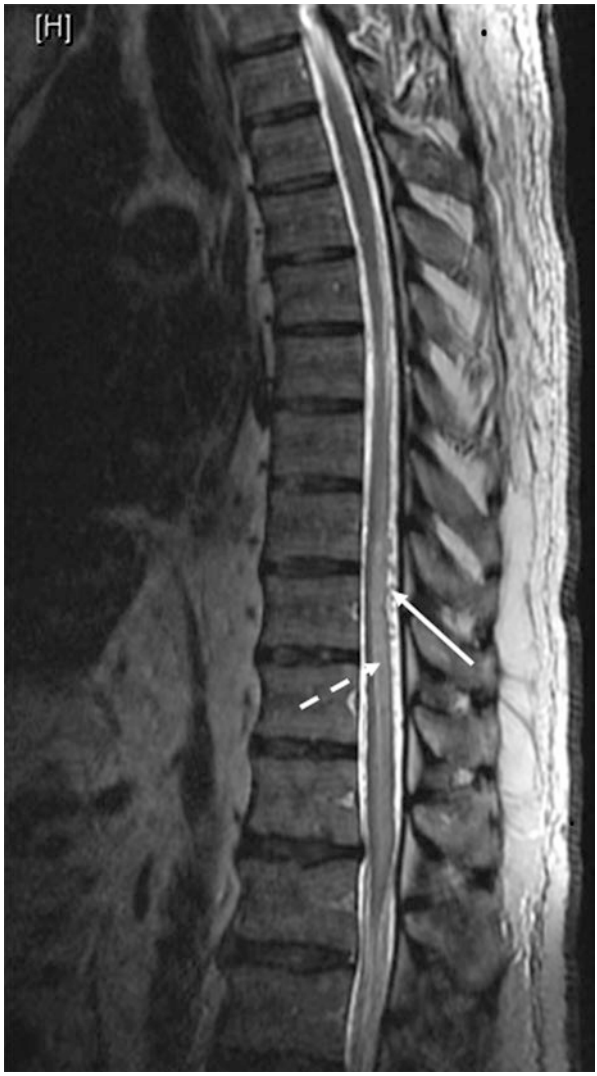

Fig. 17.3 Sagittal T2-weighted MRI of the thoracic spine shows flow voids indicative of dural fistula (solid line) with accompanying hyperintensity within the spinal cord (dashed line)

Hereditary Spastic Paraplegia (HSP)

This heterogeneous group of conditions causes lower extremity weakness, spasticity, and hyperreflexia [14]. Dysfunction may be limited to the spinal cord (simple HSP) or involve the spinal cord and other parts of the nervous system (complicated HSP). HSP may be inherited in any fashion, although autosomal dominant forms are the most common. The diagnosis may be straightforward in patients with a suggestive family history. Comprehensive genetic testing is helpful in establishing a diagnosis, though the gene mutations responsible for many cases of HSP have not yet been established.

Inflammatory Radiculopathies (Radiculitis)

Most radiculopathies are caused by physical compression of the nerve root. Inflammatory radiculopathy and polyradiculopathy are less common, but important, as they frequently reflect serious and reversible underlying medical conditions. In general, radiculitis should be considered in patients with radiculopathy, and no obvious nerve root compression or imaging studies that show inflammation of the nerve roots without obvious structural spinal disease. Spinal fluid analysis may help in the evaluation of patients with suspected radiculitis. Common causes of inflammatory radiculopathy include Lyme disease, diabetes (especially at the thoracic levels), sarcoidosis, malignant nerve root invasion, and viral infections (most commonly herpes zoster, cytomegalovirus, and herpes simplex).

Musculoskeletal Back Pain

A wide variety of musculoskeletal conditions may produce back and neck pain. Although such pain is generally self-limited, it may also be chronically disabling and lead to missed work and financial hardship. Because there are no reliable diagnostic tests for musculoskeletal back pain, it is fertile ground for malingerers. Patients with refractory musculoskeletal back pain are frequently referred to neurologists to "rule out a neurologic cause." Thus, it is essential to be able to differentiate between neurologic sources of back pain and non-neurologic ones. Typical characteristics of non-neurologic back pain include tightness, aching, swelling, point tenderness, and a lack of symptom radiation into the extremities. Paresthesia and true motor dysfunction (not give way weakness secondary to pain or poor effort) should be absent. Although most patients with musculoskeletal pain cannot be given a precise diagnosis, there are several exceptions which should be familiar to all neurologists.

Strains and Sprains

Muscle strains and ligament sprains are the most common non-neurologic causes of back pain. The patient usually provides a history of injury such as lifting a heavy suitcase or moving a piece of furniture that is followed several hours to a few days later by non-radiating, dull, aching pain. Strains and sprains are usually identified and treated by primary care physicians, but in some cases, atypical symptoms such as tingling or burning may lead to neurologic referral. A combination of rest, ice, and nonsteroidal anti-inflammatory medications generally improves symptoms in a few days.

Vertebral Fractures

Osteoporosis, trauma, and metastasis are the most important causes of spinal fractures. Unstable fractures that compromise the spinal cord or cauda equina are a medical emergency and need to be treated with immobilization and possibly with surgical stabilization. Acute compression fractures without compromise of the spinal cord may be treated with immobilization and pain relievers. Vertebroplasty is commonly performed for osteoporotic fractures but offers little relief beyond that provided by conservative measures [15, 16].

Sacroiliac Joint Dysfunction

Pain derived from the sacroiliac joints is possibly among the most common causes of lower back pain but may be unrecognized because it is not a well-defined clinical entity. Patients complain of back pain that may mimic radiculopathy because it radiates into the groin, hip, thigh, or leg. The mainstay of treatment is NSAIDs and gentle physical therapy. Local injections are reserved for patients with refractory symptoms.

Coccygodynia

Pain in the coccygeal region may mimic sacral radiculopathy or lead to evaluation for cauda equina syndrome. Although there may be a history of trauma, coccygodynia may be the result of nothing more than prolonged sitting. The diagnosis is confirmed by finding tenderness with direct manipulation of the coccyx. Treat patients with coccygodynia with cushioned seating and local steroid injections.

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Gait Disorders

18

Introduction

Falls are common in the elderly population and frequently lead to injury or hospitalization. Gait dysfunction may be the result of pathology at any level of the neuraxis; making its evaluation is among the most challenging in clinical neurology. Unlike most neurologic problems, the history is usually unhelpful: the patient may say that their legs are weak, that their legs give out on them, that they feel off balance, or simply that they fall and do not know why. The examination is usually more powerful than the history in making a diagnosis. Occasionally, you will be able to make a very accurate analysis of gait dysfunction by watching the patient walk from the waiting area to the examining room. When this is not the case, a thorough neurologic examination including formal gait analysis and provocative maneuvers will help in localizing the problem.

Natural Gait

Examine natural gait by having the patient walk up and down a long hallway. Everyone can identify a normal gait intuitively, but what is less intuitive is how to describe that gait in words. Formal gait analysis is a distinct field of biomechanics and neurophysiology, but for clinical purposes, examining and documenting the following seven components of natural gait are sufficient and effective:

- Posture. Does the patient stand up straight or are they hunched over? Are they hyperextended at the waist and neck?
- Base. Do they stand with their feet close together or is their base abnormally widened? When they walk, are the medial edges of their feet separated by more than six to eight inches?
- Initiation. When they start to walk, do they do so quickly or is there some delay?

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- Stride length. Do they appear to be taking normal-length strides or are their strides shortened?
- Stride appearance. Do their feet elevate appropriately or do they just barely clear the ground? Do they land normally or awkwardly? Do they shuffle or slap the ground with their feet? Is there any posturing of the arms?
- Stability. Do they appear stable on their feet or do they constantly seem to be at risk to fall?
- Turns. Do they require more than two or three steps to turn 180°?

Provocative Maneuvers

Performing provocative maneuvers may help to reveal subtle abnormalities that are not detected immediately by examination of natural gait.

Trendelenburg Sign and Gowers' Sign

These are two signs of proximal muscle weakness. To test for a Trendelenburg sign, observe the patient from behind as they stand on one foot: in patients with weakness of hip stabilization, the trunk will sink to the side of the elevated leg (see also Chap. 10). Gowers sign is present when a patient needs to use their arms to rise from a seated position on the floor, but it is usually more valuable in children with suspected muscular dystrophy as even normal healthy adults have difficulty performing this task. Similar information about proximal weakness may be obtained by looking for difficulty or inability to rise from a chair while their arms are folded across their chest.

Heel and Toe Walking

Distal lower extremity weakness is an important source of gait difficulty. Walking on the toes requires integrity of the gastrocnemius-soleus complex and its innervation from the tibial nerve and S1 nerve root. Walking on the heels relies on the tibialis anterior innervated by the peroneal nerve and the L4–5 nerve roots. Due to the relatively greater length of the peroneal compared to the tibial nerve, heel walking tends to be impaired earlier than toe walking in patients with polyneuropathies.

Tandem Gait

Although any cause of gait impairment may lead to difficulty with tandem gait, an inability to tandem walk is classically associated with an ataxic gait. To test tandem gait, instruct the patient to "walk the tightrope" or do the "drunk test" by placing one foot in front of the other, taking each step with their heel directly in front of the

big toe of the opposite foot. Bear in mind that both older and obese patients who are otherwise neurologically normal perform this task poorly.

Stress Gait

This test may be helpful in establishing a diagnosis of early Parkinson disease. To test stress gait, ask the patient to walk on the sides of their feet. While they are doing this, observe their hands and arms for subtle tremor or posturing indicative of extrapyramidal dysfunction.

Pull Test

This test is commonly performed when an extrapyramidal disorder is suspected. Because this test poses a serious possibility of injury, perform it with caution. Instruct the patient to stand with their feet spread slightly apart and their arms abducted approximately 15° away from their trunk. Stand behind them, and tell them that you will pull them and that they will need to maintain their balance. Prepare to catch the patient should they fall, and then briskly pull them backwards by the shoulders. They should require at most one step backwards to correct their balance. Sufficiently advanced Parkinson disease may cause postural instability, and the patient will require multiple steps to correct their balance or even fall backwards into your arms. Exercise caution in performing the pull test: if it seems unsafe to do it, then it probably is!

Romberg Sign

A Romberg sign reflects disorders of the proprioceptive or vestibulocerebellar systems. To test for a Romberg sign, first ask the patient to stand with their feet placed together and make sure that they can keep their balance. Next, instruct them to close their eyes. Most patients with proprioceptive deficits will sway when their eyes are closed. The strict definition of a positive Romberg sign, however, requires that the patient falls when this test is performed.

General Neurologic Examination

Confirm all abnormalities detected by gait observation with a thorough neurologic examination. In some cases, the general examination will disclose an explanation for gait impairment that was not uncovered by gait analysis or provocative maneuvers. It is essential to perform musculoskeletal, ophthalmologic, and peripheral vascular examinations to look for evidence of dysfunction in other organ systems that may lead to instability and falls before concluding that the source of a patient's gait abnormality is neurological.

Abnormal Gait Patterns

Frontal Gait

A patient with a frontal gait disorder initiates walking with difficulty, elevates their feet minimally, and takes small, short steps. Sometimes this pattern of gait is labeled as "apraxic," a term which is more properly reserved for disorders of *learned* movement. Frontal gait disorder is often accompanied by dementia. Common causes of frontal gait disorder include the multi-infarct state, vascular parkinsonism, and normal pressure hydrocephalus (Chaps. 4 and 13).

Spastic Gait

Chronic corticospinal tract lesions result in a spastic gait in which the affected leg is stiff and hyperextended. The leg is circumducted (swung out from the hip in an arc) rather than moved back and forth in the sagittal plane. Corticospinal tract lesions within the brain such as stroke, demyelinating disease, or brain tumor produce contralateral spasticity which also involves the arm. Lesions of the frontal convexity may affect the leg in isolation. Spastic gait is also the characteristic abnormality of patients with myelopathy (Chap. 15), in which case the two legs tend to be involved relatively symmetrically.

Parkinsonian Gait

In early Parkinson disease (PD), gait may be affected minimally or not at all (Chap. 13). The earliest abnormalities may be slightly reduced arm swing or asymmetric hand posturing or tremor which appear upon stress gait testing. Patients with fully developed PD are hunched over, initiate slowly, and take short strides. They turn slowly and require multiple steps to do so. Postural instability may be elicited by performing the pull test. Advanced PD may be associated with festination and freezing. Festination is a distinctive gait abnormality characterized by tiny steps which progressively increase in velocity to the point that the patient appears to be running in place. Freezing, as its name suggests, occurs when a patient comes to a complete stop while walking and cannot seem to reinitiate their gait.

Progressive Supranuclear Palsy (PSP) Gait

Gait difficulty and frequent falls are early features of PSP (Chap. 13). Though the natural gait is often nonspecific in its appearance, patients with PSP are classically hyperextended at the neck and trunk and fall backwards.

Ataxic Gait

Gait ataxia is characterized by veering from side to side with over- and understepping of the target. Falls and injury are perhaps less frequent than might be expected, because ataxic patients quickly realize their gross instability and avoid walking altogether. Gait ataxia is classically associated with peripheral and central lesions of the vestibulocerebellar system, though dorsal column and large-fiber peripheral nerve disorders account for the majority of gait ataxia in clinical practice.

Waddling Gait

Disorders affecting the proximal musculature, especially the hip flexors and trunk stabilizers, lead to waddling (Chap. 10). The patient is not able to elevate their legs sufficiently to clear the ground, and as a result, must shift their weight from side to side and rotate the trunk in order to make forward progress. Signs of proximal weakness which accompany waddling include the Trendelenburg sign and the Gowers sign. Common localizations of proximal muscle weakness include the muscle, neuromuscular junction, and motor neurons.

Steppage Gait

Steppage gait due to foot drop is most commonly the consequence of lesions of the motor neurons, L4 or L5 nerve roots, or peroneal nerve (Chap. 11). In order for the foot to clear the ground, a patient with dorsiflexion weakness lifts their hip and knee in an exaggerated fashion, leading to the high step which lends this gait abnormality its name. The foot strikes the ground heavily, and sometimes it is the slapping sound as the patient walks rather than the visual detection of a foot drop which is most helpful in making the diagnosis.

Antalgic Gait

Any cause of pain below the waist may produce an antalgic gait in which the patient steps gingerly on the affected side while placing the bulk of their weight on the unaffected leg. Careful musculoskeletal and neurologic assessment is needed to separate an antalgic gait from one caused by neurologic dysfunction.

Psychogenic Gait

Gait dysfunction may be the sole manifestation of malingering or conversion disorder. While the veering, unsteady, often bizarre gait seen in many patients with psychogenic gait disorders most closely resembles ataxia, psychogenic gait may mimic

any abnormal pattern. Clues to the presence of a psychogenic gait disorder include the absence of injury during falls, fluctuating severity and semiology over time, and normal ambulation when the patient thinks that they are not being observed. The diagnosis of a psychogenic gait disorder may be made, however, only after organic disease is excluded exhaustively. Tactful psychiatric evaluation and treatment is the most effective treatment for psychogenic gait disorders.

Multifactorial Gait Disorder

It may be difficult or impossible to isolate the source of gait dysfunction to a single site in the nervous system. Patients with more than one contributor are usually diagnosed with multifactorial gait disorder. This condition is particularly common in the elderly, in whom osteoarthritis, parkinsonism, cervical myelopathy, and polyneuropathy are common and frequently coexist. For patients with multifactorial gait disorder, examination of the individual components of the nervous system is generally more helpful than gait analysis. Although they may derive modest benefit from physical therapy, many patients with multifactorial gait disorder require canes, walkers, or motorized scooters.

General Recommendations for Patients with Frequent Falls

Any reversible neurologic causes of frequent falls should be identified and treated. In many cases, this is not possible, and preventive therapy becomes the mainstay of treatment. Appropriate pain treatment and correction of orthopedic infirmities may eliminate some falls or help restore normal ambulation. Counsel patients to wear sensible shoes and avoid long pant legs and dresses which may lead to tripping. Home safety evaluation reduces fall risk by uncovering easily correctable fall precipitants such as excessive clutter, poorly placed rugs, slippery surfaces, and uneven floors. Many patients require walking sticks, canes, walkers, or wheelchairs to avoid frequent falls. These should be prescribed in conjunction with a physical therapist and physiatrist.

Headache and Facial Pain

19

History

Headache is among the most common complaints evaluated by primary care physicians and neurologists. Although all neurological diagnoses are ultimately established through a carefully taken history, this is true for no condition more than it is for headache.

Epidemiology

Patient age, gender, and medical history may suggest specific headache etiologies in some instances. While the description of the actual events is more important than any single epidemiologic factor, the following associations between patient population and headache etiology are clinically useful:

- Patients older than 55 are at risk for temporal arteritis.
- Young women are the population that is most likely to have new-onset migraines.
- Middle-aged men are susceptible to cluster headaches.
- Obese young and middle-aged women are the patients most likely to have pseudotumor cerebri.
- Puerperal women and those with hypercoagulable states are at greatest risk for cerebral venous sinus thrombosis.

Location

Because most headaches are frontal or holocranial, location may not be particularly helpful in establishing headache etiology. Temporal and parietal headaches are also nonspecific. Occipital or nuchal headaches are most commonly tension headaches

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or occipital neuralgia. Common causes of unilateral retro-orbital headaches include migraine, cluster headaches, and paroxysmal hemicrania.

Character

Character is frequently the most helpful factor in headache classification. Dullness and squeezing are typical features of tension headaches but are also common in many other headache types, including those caused by dangerous conditions such as brain tumors, temporal arteritis, and pseudotumor cerebri. Throbbing and pulsation are the typical qualities of migraines and other vascular headaches. Sharp, stabbing pain is most typical of the trigeminal autonomic cephalgias and neuralgiform headaches.

Rapidity of Onset

Most headaches develop over minutes to hours. Sudden-onset, severe headaches require immediate attention, as they may represent life-threatening neurological emergencies such as subarachnoid hemorrhage, carotid artery dissection, or pituitary apoplexy.

Duration

Headache duration often has limited value in establishing a diagnosis, as most headaches can last for half an hour at a time or for days on end. Important exceptions to this rule include cluster headaches and paroxysmal hemicrania which are very brief, usually lasting for several minutes at a time, and neuralgiform headaches which last for just seconds. Although headache duration may not help to classify the type of headache, it is often important in establishing headache severity and in determining the need for treatment.

Diurnal Variation

Most headaches, including tension headaches and migraines, develop in the late morning or early afternoon. Exceptions include cluster headaches and headaches caused by increased intracranial pressure, which are usually worse at night and may awaken a patient from sleep.

Associated Symptoms

Aura

Symptoms which accompany headache are often the ones which help to cinch the diagnosis. This is perhaps most true for migraines, in which the headaches may be somewhat nonspecific, and the diagnosis is bolstered by the presence of an aura. An aura is a neurologic symptom which begins several minutes prior to migraine onset (or sometimes while the headache is developing) and most commonly takes the form of visual hallucinations of flashing lights, lightning strikes, distortions in size such as micropsia and macropsia, wavy lines, or fortification spectra (hallucinations which are named for their resemblance to medieval castle wall layouts). Auras are not restricted to vision and may have sensorimotor manifestations including tingling, weakness, and numbness. Aura symptoms characteristically spread over 15–20 minutes, which distinguishes them from stroke (sudden-onset symptoms) and seizure (symptoms which march over seconds).

Other Neurologic Symptoms

Sudden unilateral or sequential visual loss is a worrisome symptom that suggests temporal arteritis. Seizures or other rapidly developing, fixed neurologic deficits point to serious pathologies including intracranial hemorrhage, mass lesions, venous sinus thrombosis, encephalitis, or hypertensive encephalopathy.

Systemic Symptoms

Nausea, vomiting, photophobia, and phonophobia frequently accompany migraine. Conjunctival injection, lacrimation, and rhinorrhea are features of the trigeminal autonomic cephalgias. Visual loss, scalp tenderness, jaw claudication, low-grade fever, and proximal muscle tenderness are all systemic symptoms of temporal arteritis.

Exacerbating Factors

High stress levels worsen almost all headaches. Actions which strain the neck including excessive head turning, staring at a computer screen all day long, and even sleeping in the wrong position tend to precipitate tension headaches. Not eating, poor sleep, excessive caffeine intake or caffeine withdrawal, the menstrual period, chocolate, cheese, and red wine all exacerbate migraine headaches. Lying flat and sleeping worsen headaches due to increased intracranial pressure. Standing precipitates or worsens low-pressure headaches secondary to spontaneous intracranial hypotension or lumbar puncture.

Alleviating Factors

Other than medications, patients describe a variety of different factors that alleviate their headaches. Rest in a quiet, dark room improves migraines. Loosening a tight necktie, massage, or applying heat often helps tension headaches. Lying down improves low-pressure headaches, while standing up improves headaches due to increased intracranial pressure.

Frequency

Cluster headaches occur multiple times within a span of a few weeks or months. Chronic daily headache occurs at least 15 days each month. In many cases headache frequency is not very helpful in establishing a specific diagnosis. It may, however, be important in determining which patients require only symptomatic treatment and which ones will need prophylactic treatment. If there is any doubt about the actual headache frequency, instruct the patient to keep a headache diary.

Severity and Disability Level

While severity and disability level do not help to classify headaches accurately, they help to determine appropriate treatment. Grading headache severity on a scale of one to ten is often used in practice, but this rating system is frequently unhelpful, as each patient has their own pain "nocistat" which reflects numerous psychosocial factors. One rule of thumb is that a patient who reports that they have a high pain tolerance almost never does. While I do employ numeric rating scales in practice, the best way to establish pain severity is to ask the patient whether they ever miss work or school because of the headaches. Frequent interference with daily commitments mandates aggressive headache treatment.

Prior Evaluation and Treatment

Many patients undergo neuroimaging or other laboratory studies prior to neurological consultation, and it is necessary to review these studies before determining the need for additional ones. Patients usually try to treat their headaches with over-the-counter medications such as acetaminophen, ibuprofen, and naproxen. Primary care physicians often prescribe triptans for migraine patients before obtaining a neurologist's assistance, and some even feel comfortable prescribing a prophylactic agent such as propranolol, amitriptyline, or topiramate. Because many patients who seek neurological attention for headache management have

refractory headaches, it is important to maintain a log detailing a patient's response to and tolerance of all medications.

Dangerous Headaches

Although most headaches are benign and may be managed safely in the outpatient setting, some headaches are due to dangerous and sometimes life-threatening conditions. Headache red flags include sudden onset, fixed neurologic symptoms, accompanying seizures, and change in headache character. Headaches in patients with known cancer or immunosuppression are also worrisome. Patients older than 55 with new-onset headache are at risk for temporal arteritis. Dangerous headaches may be divided into sudden-onset or "thunderclap" headaches and chronic headaches.

Sudden-Onset Dangerous Headache Syndromes

Subarachnoid Hemorrhage (SAH)

SAH due to aneurysmal rupture is among the most serious of neurological emergencies. The concept that "the worst headache of my life" and SAH headache are synonymous is widely known but misleading. Every person will eventually have the worst headache of their life, and SAH will be the cause in only a small fraction [1]. While SAH headaches are usually extremely severe, it is their rapid onset rather than their intensity that defines them. SAH headache builds to a climax in just a few seconds and is sufficiently jarring to stop the patient in their tracks. Vomiting and stiff neck often accompany the headache, and in many cases, seizure and loss of consciousness occur at onset. Some patients may have a sentinel headache due to leakage of a small amount of blood from the aneurysm preceding the SAH by up to 2 weeks. The exact incidence of sentinel headache preceding SAH is unknown but may be as high as 40% [2].

Urgent and thorough evaluation is necessary for all patients with suspected SAH. Non-contrast head CT is extremely powerful in detecting acute subarachnoid blood (Fig. 19.1), but the likelihood of finding subarachnoid blood after SAH decreases with time (Adams et al. 1983; van Gijn and van Dongen 1982) [3, 4]:

- 95% between 0 and 1 days after rupture
- 90% between 1 and 2 days after rupture
- 85% at 5 days after rupture
- 50% at 1 week after rupture
- 30% at 2 weeks after rupture
- Almost zero at any time after 3 weeks

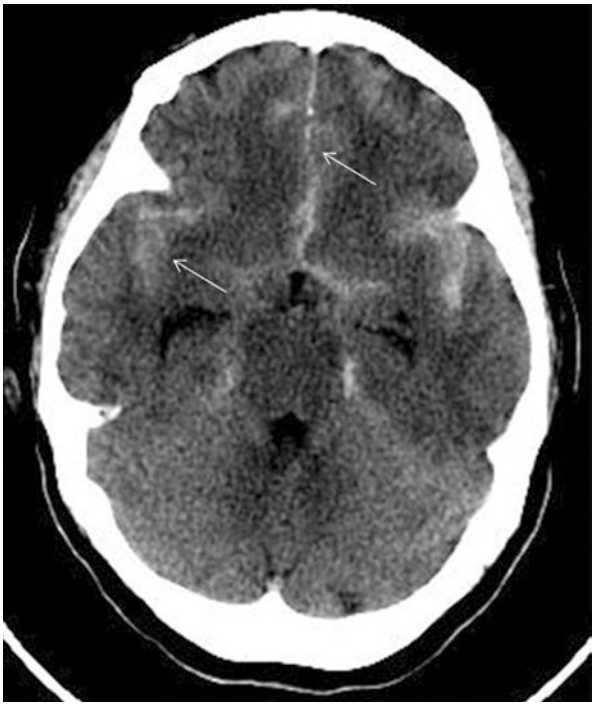

Fig. 19.1 Non-contrast head CT demonstrating subarachnoid hemorrhage

Although the sensitivity of CT scan is very high in the first few hours after SAH, the penalty for missing the diagnosis is extreme. There are two options in patients who have presentations consistent with SAH and negative non-contrast head CT scans:

- Lumbar puncture. The advantages of lumbar puncture are high sensitivity and lack of exposure to radiation. Disadvantages are discomfort, post-LP headache (see below), technical challenges of the procedure (see Chap. 1), and difficulty with interpreting the CSF sample. Visual inspection of the CSF may allow SAH diagnosis, but in some cases, it may be difficult to differentiate between blood due a traumatic lumbar puncture and SAH. The best way to distinguish between SAH and a traumatic tap is by using spectrophotometry to identify xanthochromia, reflective of hemolysis within the CSF [5].
- Head CT angiography (CTA). The advantages of CTA are lack of pain and clear definition of an aneurysm if one is present. Disadvantages are contrast dye exposure and lower sensitivity compared to LP. Modest specificity is also a challenge: because small aneurysms are identified commonly on CTA, their clinical relevance is not always certain, and patients may undergo unnecessary conventional angiography or even neurosurgical intervention due to a small, incidental aneurysm.

Overall, the probability of identifying SAH in a patient with a suggestive history and normal non-contrast head CT is low. In a study of 2248 patients with symptoms suggestive of SAH who underwent lumbar puncture, 4.8% had blood in their CSF,

and 0.4% had aneurysms on subsequent imaging [6]. The trend and my personal practice are to perform non-contrast head CT first, CTA if the CT is negative, and then offer LP only if the clinical suspicion for SAH remains high after a negative CTA. The likelihood of missing an aneurysm using this algorithm is extremely small [7].

Any patient with evidence for non-traumatic SAH by CT, CTA, or LP should undergo conventional angiography (see also Box 19.1). Patients with confirmed subarachnoid hemorrhage should be evaluated by a neurosurgeon for possible surgical clipping or endovascular coiling of the responsible aneurysm. Because aneurysmal SAH is principally a neurosurgical disease, it will not be discussed further here. The interested reader is referred to the American Heart Association's Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage [8].

Box 19.1 Unruptured Intracranial Aneurysms

Intracranial aneurysms come to clinical attention most often when they rupture, resulting in SAH. Unruptured aneurysms are almost always asymptomatic and noted when neuroimaging is performed to evaluate headache, memory loss, or another neurologic complaint. An unruptured aneurysm justifiably creates anxiety for both the patient and referring physician. Management decisions are made based on the risk of aneurysm rupture and the likelihood of complications from intervention. Pooled prospective cohort studies indicate a 1.4% annual risk and 3.4% 5-year risk of rupture [31]. Larger aneurysms and those derived from the middle cerebral artery and posterior circulation are likely to rupture. Patient age greater than 70, history of hypertension, and history of previous aneurysmal rupture all increase the risk of rupture.

This risk of aneurysmal rupture must be weighed against the risk of surgical or endovascular interventions. Based on data from the International Study of Unruptured Intracranial Aneurysms (ISUIA), the 1-year risk for death or poor neurologic outcome is approximately 13% in patients undergoing open surgical clipping and 9% in patients undergoing endovascular coiling [32]. As might be predicted, older age, larger aneurysm size, and posterior circulation location are all associated with a greater likelihood of poor outcome. Patients who undergo endovascular procedures are also at risk for incomplete obliteration of the aneurysm.

Ultimately the decision to intervene on an unruptured intracranial aneurysm must be made on an individual basis after careful discussion with the patient and neurosurgeon. For many aneurysms, the risk of rupture is extremely small, and surgical intervention is a greater risk than rupture. The patients with the most obvious benefit from intervention are younger patients with aneurysms between 7 and 24 mm in diameter. Patients with aneurysms smaller than 7 mm in diameter or asymptomatic intracavernous aneurysms should not undergo intervention in most cases. For patients who do not undergo intervention, repeat MRA or CTA to monitor for aneurysmal growth every 6–12 months for 3 years is reasonable. Evidence for aneurysmal growth on serial imaging studies should prompt stronger consideration of intervention.

Carotid Artery Dissection

Dissection of the cervical carotid artery may produce a sudden-onset, severe headache. Trauma, especially that secondary to vigorous exercise, yoga, or chiropractic manipulation, is commonly identified as the precipitant. The headache of carotid dissection is typically unilateral, throbbing, and retrobulbar and may therefore be misdiagnosed as migraine. When accompanied by ipsilateral Horner syndrome (due to involvement of the oculosympathetic fibers which ascend into the skull with the internal carotid artery), it may be misdiagnosed as cluster headache. CTA or MRA of the neck confirm the diagnosis. The most important problem posed by carotid artery dissection is not the headache, but rather the possibility of embolic stroke: thrombus may form at the intimal flap of a dissection, and small clots may then be thrown distally into the anterior circulation. There is no clear difference in stroke prevention between anticoagulation and antiplatelet therapy, and either treatment option is acceptable [9].

Pituitary Apoplexy

Pituitary apoplexy occurs most often when a rapidly growing pituitary adenoma outstrips its vascular supply, leading to infarction of the pituitary gland. The headache of pituitary apoplexy is sudden in onset and resembles that of SAH. Neurologic signs that accompany pituitary apoplexy include bitemporal hemianopsia due to compression of the optic chiasm and ophthalmoplegia due to involvement of the ocular motor nerves in the adjacent cavernous sinus. The most urgent problem facing a patient with pituitary apoplexy is hypotension, which results from the acute loss of adrenocorticotropic hormone. Treat patients with suspected pituitary apoplexy with dexamethasone (4 mg IV) to prevent adrenal insufficiency and intravenous fluid boluses to maintain adequate blood pressure. Definitive management of pituitary apoplexy requires the assistance of an endocrinologist and possibly a neurosurgeon.

Reversible Cerebral Vasoconstriction Syndrome (RCVS)

RCVS presents with a sudden-onset, thunderclap headache similar to that seen in aneurysmal SAH [10]. Some patients have a history of exposure to vasoconstricting drugs such as triptans or amphetamines, but in most patients, a clear precipitant cannot be identified. Pregnant women are at increased risk of developing RCVS. Headaches may last for several hours at a time and recur over a period of weeks. The diagnosis is established by finding vasoconstriction on a cerebral vascular imaging study, usually MRA or CTA. RCVS can lead to infarction, hemorrhage, or seizures, but most patients have good outcomes even in the presence of a stroke. Although calcium channel blockers and corticosteroids are often prescribed as treatments, there is no clear benefit for any therapy, as vasoconstriction usually resolves over time.

Migraine

Only a minority of sudden-onset, severe headaches which bring patients to the emergency room are due to subarachnoid hemorrhage [11]. Although migraine likely accounts for most of the balance, it should be considered a diagnosis of exclusion.

Subacute and Chronic Dangerous Headache Syndromes

Temporal Arteritis

The headache of temporal arteritis may have nonspecific features and therefore masquerade as a more benign disorder such as migraine or tension headache. Temporal arteritis is vanishingly rare in patients younger than 55. Despite its name, the headaches do not occur exclusively in a temporal distribution. Clues to the diagnosis include monocular visual loss, jaw claudication (pain with chewing), scalp tenderness, and fever. Polymyalgia rheumatica, characterized by pain in the shoulders and hips, frequently accompanies temporal arteritis. Firmness, tenderness, and induration of the superficial temporal arteries are classical but not universal physical examination findings. Because visual loss is the principal danger of temporal arteritis, it is discussed further in Chap. 5.

Cerebral Venous Sinus Thrombosis (CVST)

CVST produces a variety of signs and symptoms including headache, seizures, encephalopathy, and venous strokes. The condition often takes several weeks to develop, and in its earliest stages, a nonspecific headache which resembles migraine or tension headache may be the only problem. Women in the puerperium and those who use oral contraceptives are at increased risk for cerebral venous sinus thrombosis. Sepsis, malignancy, dehydration, and hypercoagulable states are other important risk factors. Neurological examination may be entirely normal, may show an encephalopathy, or may show focal signs reflecting a venous stroke. Contralateral leg weakness due to superior sagittal sinus thrombosis is particularly suggestive of stroke due to CVST. The best-known neuroimaging finding in CVST (though often absent) is the positive delta sign on contrast-enhanced CT scan, which indicates collateral channels surrounding a torcular thrombus. CT scan may also show hemorrhagic infarction or cerebral edema. In milder cases, the diagnosis is made only with the aid of MR venography. Anticoagulation with intravenous heparin or low-molecular weight heparin is recommended for patients with cerebral venous sinus thrombosis and should be provided even if patients have hemorrhagic strokes. Anticoagulation should be continued for 6–12 months; a shorter course may be appropriate for patients with risk factors for venous sinus thrombosis that are expected to resolve. Dedicated management of increased intracranial pressure (Chap. 2), seizures (Chap. 20), and stroke (Chap. 21) may be required.

Meningitis

Bacterial and viral meningitis are potentially serious neurologic emergencies characterized by fever and sometimes by headache and stiff neck. Headache may be the most prominent or solitary symptom in immunocompromised patients. Further evaluation and treatment of meningitis is discussed in Chap. 1.

Headache Secondary to Mass Lesions

Headaches from intracranial masses are classically worse while recumbent, may awaken the patient in the middle of the night, and may be associated with focal

neurological signs or seizures. In clinical practice, however, these features are uncommon, as most patients with brain tumors (and other mass lesions) have headaches that resemble tension headaches or migraines [12]. Evaluation of intracranial mass lesions is discussed further in Chap. 23.

Pseudotumor Cerebri (Idiopathic Intracranial Hypertension)

Pseudotumor cerebri is a syndrome of uncertain etiology characterized by headache and visual loss. Because it is widely known that young, obese women are affected most frequently, the diagnosis may be missed in other groups. Precipitants of pseudotumor other than obesity include excess vitamin A, lithium, tetracyclines, and both steroid administration and withdrawal. The headaches of pseudotumor cerebri are nonspecific and usually resemble tension headaches. Visual symptoms include blurriness, transient orthostatic visual loss, visual distortion, and photopsias. Other symptoms of pseudotumor cerebri include pulsatile tinnitus, dizziness, and neck pain. As pseudotumor progresses, visual symptoms become more constant, and blindness may occur if increased intracranial pressure goes untreated. The evaluation of pseudotumor cerebri should include the following:

1. CT or MRI of the brain to exclude the possibility of true tumor or another cause of increased intracranial pressure
2. Dilated funduscopic examination to look for papilledema (Fig. 19.2)
3. Lumbar puncture showing an opening pressure of at least 20 cm H_20
4. Formal perimetry to determine the extent of visual field loss

Obviously, the first step in treating pseudotumor cerebri is to discontinue any responsible medications. Although weight loss may help reverse many of the symptoms of pseudotumor, most patients are not able to lose the weight necessary to

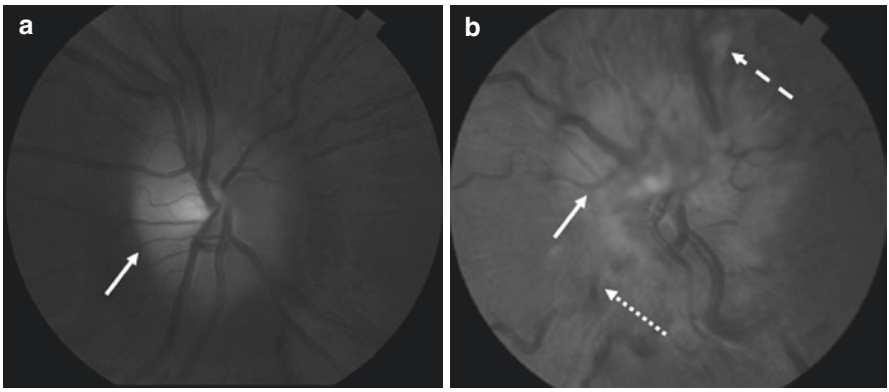

Fig. 19.2 Papilledema in patients with pseudotumor cerebri. In early pseudotumor cerebri, (**a**) there is mild elevation of the optic disk (solid arrow). In severe papilledema (**b**) there is massive disk elevation (solid arrow) with peripapillary cotton wool spots (dashed arrow) and splinter hemorrhages (dotted arrow). (Images courtesy of Dr. Nurhan Torun)

allow a meaningful improvement. The mainstay of medical treatment is acetazolamide, administered at doses ranging from 250 mg bid to 1000 mg bid. Perioral and acral paresthesias may be dose-limiting side effects of this medication. If acetazolamide is not effective or tolerated, the next line of treatment is serial lumbar punctures, which are impractical for doctor and patient alike. If serial lumbar punctures provide consistent relief, then consider ventriculoperitoneal shunting as a more permanent method to remove cerebrospinal fluid. Patients with rapidly progressive visual loss may need optic nerve sheath defenestration to prevent complete blindness. Bariatric surgery to address obesity may be valuable as a long-term treatment [13].

Hypertensive Encephalopathy

Despite popular belief, garden variety essential hypertension does not lead to headaches. Hypertensive encephalopathy (a cause of posterior reversible encephalopathy syndrome or PRES, Chap. 1), however, occurs in patients with either very high blood pressure or rapid increases in blood pressure. In addition to headaches, patients with hypertensive encephalopathy may be confused, seize, lose their vision, or have essentially any focal neurological finding. Hypertensive encephalopathy is frequently accompanied by other problems related to malignant hypertension including angina, pulmonary edema, and renal failure. It is imperative to rapidly lower the blood pressure in patients with hypertensive encephalopathy in order to prevent irreversible neurological and systemic damage.

"Benign" Headaches

Migraine Headaches

Many patients describe any severe headache as a migraine, even if they have tension or cluster headaches. It is, therefore, essential to ask the patient what they mean by migraine and ensure that their self-diagnosis is correct. In its most typical form, migraine is characterized by a throbbing, unilateral headache associated with nausea, vomiting, photophobia, and phonophobia. It is common but not universal for migraineurs to describe aura symptoms including visual loss, scintillating scotoma, tingling in the extremities, and even weakness resembling stroke. These aura symptoms most often precede the onset of headache by several minutes but may occur simultaneous to it or start after the headache in rare cases. Aura symptoms typically last for 20–30 minutes but can last for a few hours in rare cases. Premonitory symptoms such as fatigue, irritability, food cravings, and frequent yawning may precede attacks of migraines by hours or days. Most patients with migraine experience their first attacks during their teens or early 20s. The disorder is three times as common in women as it is in men. Migraines do not usually begin in patients over the age of 50, and other causes of headache should be excluded in this patient population before diagnosing migraine. The diagnosis is ultimately made on clinical grounds, with neuroimaging studies being used to exclude other more serious conditions.

Table 19.1 Oral triptans

	Starting dose	Maximum daily dose
Almotriptan	6.25 mg	25 mg
Eletriptan	20 mg	80 mg
Frovatriptan	2.5 mg	7.5 mg
Naratriptan	2.5 mg	5 mg
Rizatriptan	5 mg	30 mg
Sumatriptan	25 mg	200 mg
Zolmitriptan	2.5 mg	10 mg

The first step in treating migraines is lifestyle modification. Ask the patient about migraine precipitants such as sleep deprivation, stress, not eating, menstruation, and foods such as chocolate, cheese, caffeine, and red wine. A headache diary is helpful to keep track of these exposures and the resulting migraine frequency. Lifestyle modifications may reduce headache frequency considerably or even cure the headaches in a very small minority, but medications are usually required. Most patients with migraines respond to an over-the-counter analgesic such as acetaminophen, ibuprofen, or naproxen and never come to the attention of a neurologist. The usual first-line agent in patients who do not respond to one of these medications is a triptan (serotonin 1B/1D agonist). Triptans are effective in aborting migraines if given early enough in an attack: ideally, a patient should take their triptan within 30 minutes of developing a headache, but they may still benefit up to 3 hours after headache onset. The main side effects of triptans include chest pain, flushing, nausea, and grogginess. They should be avoided in patients with cardiovascular or cerebrovascular disease and in those who are taking monoamine oxidase inhibitors. Table 19.1 summarizes oral triptan dosing. Patients with disabling migraine-related nausea who cannot tolerate oral medications may benefit from intranasal sumatriptan (10–20 mg) or zolmitriptan (2.5–5 mg) or subcutaneous sumatriptan (4–6 mg). Triptans are often more effective when used in combination with nonsteroidal anti-inflammatory drugs, and a combination of sumatriptan/naproxen (85 mg/500 mg) is available [14]. It is important to monitor for excessive triptan use, as this may precipitate chronic daily headaches. Failure to respond to one triptan does not necessarily mean that a patient will not respond to a different one.

Some patients will have migraines of such frequency and severity that they will require a prophylactic medication. In general, consider prophylactic medications for patients with more than three migraines a month or for patients with attacks that interfere with their ability to work or to attend school. Each patient will have a threshold at which they will think that prophylactic therapy is appropriate. Table 19.2 contains a summary of some of the commonly used migraine prophylactic agents. There is no single best agent for all patients, and a prophylactic medication should be chosen based on side effect profile and potential interactions with other medications and medical conditions. There is a temptation to switch prophylactic medications when they are not effective immediately. I try a prophylactic agent for 3 months before declaring treatment failure. Screen for medication non-compliance, as is a frequent reason for continued migraines.

Table 19.2 Migraine prophylactic agents

Medication	Class	Starting dose	Typical daily dose	Side effects
Amitriptyline. Nortriptyline	Antidepressant	25 mg qhs	50–100 mg qhs	Fatigue, dry mouth, cardiac arrhythmia
Feverfew	Herbal supplement	50 mg qd	50–300 mg qd	Gastrointestinal upset, palpitations
Gabapentin	Antiepileptic drug	100 mg tid	300–600 mg tid	Minimal beyond sedation and sometimes dizziness
Magnesium citrate	Mineral	400 mg qd	400 mg qd	Abdominal cramping, diarrhea
Mirtazapine	Antidepressant	15 mg	15–30 mg qhs	Weight gain, fatigue
Propranolol extended release	Antihypertensive	60 qhs	60–240 mg qhs	Hypotension, bradycardia, fatigue, depression
Riboflavin	Vitamin	200 mg bid	200 mg bid	Urinary discoloration
Topiramate	Antiepileptic	25 mg qhs	50–200 mg qhs	Weight loss, anomia, nephrolithiasis, acral paresthesias
Valproic acid	Antiepileptic	250 mg bid	250–1000 mg qhs	Tremor, thrombocytopenia, pancreatitis, hyperammonemia, weight gain, hair loss
Venlafaxine extended release	Antidepressant	75 mg qd	75–300 mg qd	Dizziness, nausea
Verapamil extended release	Antihypertensive	120 mg qhs	120–240 mg qhs	Bradycardia, hypotension

For patients with persistent disabling migraines despite multiple prophylactic medication trials, botulinum toxin injections and the CGRP antagonists erenumab (70–140 mg SC qmonth), fremanezumab (225 mg SC qmonth), and galcanezumab (240 mg SC loading dose followed by 120 mg SC qmonth) are options [15–17].

Perimenstrual migraines are those which occur with greater frequency around the time of menstruation. The diagnosis is established by examining a patient's headache diary and finding that the frequency of migraines is two to three times greater in the several days surrounding the menstrual period than at other times of the month. Symptomatic treatment with triptans may be helpful, but triptans are often more effective when used as prophylactic therapy for perimenstrual migraines: frovatriptan 2.5 mg bid or naratriptan 1 mg bid reduce the incidence of migraines when started 2–3 days before anticipated menstruation and continued until 3 days after menstruation [18, 19]. Another prophylactic option is estradiol 1.5 mg applied transdermally starting 2 days prior to anticipated menstruation for a total of 7 days [20, 21].

Tension Headaches

Tension headaches are the most common type of headaches. They are characterized by bifrontal, holocranial, nuchal, or occipital squeezing or tightness. Severe tension headaches may be accompanied by nausea and vomiting, symptoms which are more typically associated with migraines. Precipitants include neck strain, sitting still for a prolonged time, and sleeping in an awkward position. While most tension headaches respond to treatment with mild analgesics such as acetaminophen or ibuprofen, those which are severe enough to cause a patient to seek neurological attention are usually refractory to such medications. Heat application and stretching exercises may help. Muscle relaxants such as diazepam (2–5 mg tid), metaxalone (400–800 mg bid), baclofen (10–40 mg bid), or cyclobenzaprine (5–10 mg tid) are often helpful. For patients with refractory tension headaches, trigger point injections in the cervical paraspinal muscles, occipital muscles, and trapezii may relieve pain.

Trigeminal Autonomic Cephalalgias (TACs)

The TACs are a group of disorders characterized by unilateral headaches with autonomic features including conjunctival injection, tearing, and rhinorrhea. They are typically short in duration and occur several or many times in a brief stretch. The most common of the TACs are cluster headache, paroxysmal hemicranias, and short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing (SUNCT).

Cluster Headache

The typical cluster headache patient is a middle-aged man who is awakened from sleep by a severe, retro-orbital headache. The headache lasts for seconds to minutes at a time and is associated with conjunctival injection, tearing, and rhinorrhea. Ipsilateral Horner syndrome is a frequent finding. Unlike migraine headaches in which the patient attempts to remain still, patients with cluster headaches often pace back and forth, clutching at one side of their head or eye. Cluster headaches derive their name from the fact that they occur in clusters of multiple headaches, night-after-night for several weeks. A patient may note predominance of clusters during specific seasons. The differential diagnosis of cluster headaches includes carotid artery dissection, paroxysmal hemicrania, and sometimes subarachnoid or intraparenchymal hemorrhage. In most cases, the diagnosis is made by the clinical features alone. Acute treatment options for cluster headaches include inhaled 100% oxygen, subcutaneous sumatriptan (see above), and intranasal lidocaine (1 mL 4% solution). The two most effective prophylactic agents are verapamil (240–720 mg qd) and lithium (300 mg bid, titrated to 600 mg bid with a goal plasma level between 0.6 and 1.2 mmol/L). Be cautious when prescribing lithium, as it may produce side effects including tremor, ataxia, hyperthyroidism, and renal failure.

Paroxysmal Hemicrania

This headache disorder is most frequent in young women and is sometimes confused with migraine or cluster headache. The headache is sharp, stabbing, and throbbing, usually lasts under 30 minutes at a time, and recurs multiple times during a day. A distinguishing feature of paroxysmal hemicrania is its responsiveness to indomethacin at doses of 25–100 mg bid-tid. Paroxysmal hemicrania may be either episodic, in which events stop after a few weeks or months or chronic, in which events recur frequently.

Short-Lasting Unilateral Neuralgiform Headaches with Conjunctival Injection and Tearing (SUNCT)

The headaches of SUNCT are usually severe, periorbital, and last for a few seconds to a few minutes at a time. Conjunctival injection and tearing occur with the headaches, giving the disorder its name. SUNCT is most common in middle-aged patients. They occur many times (often more than 100) per day and respond poorly to medications used for migraines or other trigeminal autonomic cephalalgias. Anticonvulsants including carbamazepine, gabapentin, and lamotrigine may be effective.

Visual Strain Headaches

Visual strain headaches are common and may be confused with primary headache disorders. Following excessive reading, television watching, or computer work, patients note an aching or burning pain behind or above the eyes accompanied by ocular fatigue and sometimes by conjunctival injection. The pain may radiate into the forehead or temples and be confused with migraine or tension headaches. Correction of refractive errors or other visual abnormalities often reduces the frequency and severity of these headaches.

Medication-Related Headache

Headache is listed as a side effect in the prescribing information of almost every medication. Common offenders include beta-blockers, cyclosporine, dipyridamole, isotretinoin, and vasodilators such as nitroglycerin. It is often difficult to distinguish between headaches caused by medication and those which are caused by a primary headache disorder. A brief trial of withdrawing the presumed precipitant may be warranted.

Post-lumbar Puncture Headaches

Severe headaches caused by persistent leakage of cerebrospinal fluid affect approximately 20–30% of patients who have undergone lumbar puncture. The headaches characteristically develop between 1 and 2 days after the lumbar puncture is

performed, involve the frontal or occipital-nuchal regions bilaterally, appear within seconds of assuming an upright position, and are relieved (often completely) by lying flat. The first step in treating these headaches is to instruct the patient to lie flat for 24 hours and drink caffeinated, carbonated beverages. If symptoms do not resolve, try the combination of caffeine/butalbital/acetaminophen but for no more than 72 hours, as chronic use of this medication may worsen the headaches. For patients who do not respond to conservative therapy, an epidural blood patch which promotes sealing of the dural tear is almost always effective.

Spontaneous Intracranial Hypotension (SIH)

SIH is caused, in most cases, by a traumatic spinal dural tear with CSF leakage [22]. The characteristic holocranial or occipital headache develops suddenly and occurs when the patient is upright and improves or resolves completely when they lie flat. The patient may report vertigo and diplopia, and some patients develop sixth nerve palsies. Neuroimaging findings include sagging of the cerebellar tonsils and diffuse pachymeningeal enhancement (Fig. 19.3). Localizing the dural tear within the spine is more challenging and requires neuroradiologic expertise to perform targeted spine MRI and digital subtraction myelography [23]. The first line of treatment of

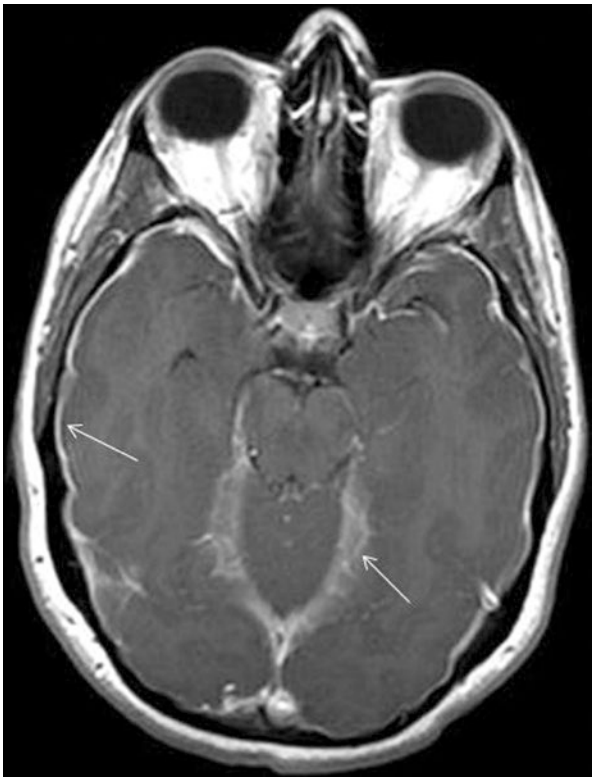

Fig. 19.3 Axial FLAIR MRI shows diffuse meningeal enhancement in a patient with spontaneous intracranial hypotension

SIH is aggressive hydration, caffeine, and epidural blood patch. In some cases, epidural blood patches at multiple levels of the spine are needed. Patients with refractory symptoms and radiologically confirmed spinal dural tears should undergo surgical closure [24].

Occipital Neuralgia

Occipital neuralgia is an uncommon disorder characterized by brief, intermittent, stabbing pains which radiate from the nuchal region into the occipital region. Attacks are generally unilateral, may occur many times per day, and may be quite disabling. Physical examination is usually normal, and the diagnosis rests on the clinical history. Occipital nerve blocks may be used for both diagnostic and therapeutic purposes [25]. Medications used for trigeminal neuralgia (see below) may help in some cases. MRI studies of the upper cervical spine (sensory fibers over the occiput are derived from the C2 and C3 nerve roots) and brain may be considered for patients who do not improve with nerve blocks, who have continuous rather than intermittent symptoms, and who have fixed sensory loss.

Status Migrainosus

Status migrainosus is defined as a debilitating migraine attack lasting for more than 72 hours [26]. It seldom occurs as the first manifestation of migraine, and it usually does not affect patients with mild, infrequent headaches. Precipitants include noncompliance with prophylactic medications, stress, poor sleep, and head trauma. Treating status migrainosus is often a difficult task, and it is important to be patient when approaching this problem. Depending on the severity of symptoms, the following interventions may be necessary:

1. Basic supportive care. Place the patient in a dark, quiet room and obtain intravenous access to administer medications and replace fluids. Because patients with status migrainosus are usually bedbound, provide prophylaxis against deep venous thrombosis as needed.
2. Antiemetic agents. It is important to control the severe nausea and vomiting which often accompany status migrainosus. Some antiemetics have the additional benefit of reducing head pain. Commonly prescribed antiemetics include:
   (a) Promethazine 25–50 mg IV q6h
   (b) Prochlorperazine 5–10 mg IV q6h or 25 mg PR q6h
   (c) Metoclopramide 5–10 mg IV q6h
   (d) Ondansetron 4–8 mg IV q6h
3. Acute pain control.
   (a) Ketorolac (15–30 mg IV q6-8h) is a powerful nonsteroidal anti-inflammatory drug that is often effective for patients with status migrainosus. It may be used safely for only 48–72 hours because prolonged use can cause gastrointestinal ulceration.

(b) Intravenous narcotics are another option for acute pain treatment. Battles between migraineur and doctor over narcotic selection and dosage are frequent. Fast-acting, short-lasting agents such as morphine, oxycodone, and hydromorphone must be used sparingly in favor of longer-acting formulations. Patient-controlled anesthesia (PCA) may be necessary in patients in whom oral sustained-release morphine or oxycodone prove ineffective or intolerable. PCA should be avoided unless absolutely necessary.
(c) Valproate 500–1000 mg IV may be effective for some patients who have not responded to other agents.

4. Migraine abortive agents. Triptans are ineffective by the time a patient meets the operational definition for status migrainosus. Dihydroergotamine (1 mg IV), however, is a serotonin 1B/1D agonist which may be an effective abortive agent, even after 72 hours of symptoms.
5. Sleep aids. In many cases, the best way to break an acute migraine attack is with sleep. Diazepam (5–10 mg PO or IV) is often effective as a sleep aid and in helping to resolve status migrainosus.
6. Steroids. Short courses of prednisone (60 mg PO qd) or dexamethasone (10 mg IV followed by 4–6 mg q6h) are often employed for status migrainosus, though the evidence for their effectiveness is modest.
7. Other therapies. Conventional medical treatment often fails to completely abort status migrainosus. Additional options should this occur include trigger point injections, lidocaine or ketamine infusions, biofeedback, acupuncture, and psychiatric evaluation.

Once an attack of status migrainosus is under control, the patient must be transitioned to a regimen that is appropriate for outpatient use. Taper and then discontinue antiemetics, narcotics, and sleeping aids as tolerated. Prophylactic regimens must be augmented to prevent recurrence of status migrainosus.

Chronic Daily Headache (CDH)

Chronic daily headache (CDH) is a syndrome defined by headaches that occur at least 15 days per month and last for at least 4 hours per day [27]. The headaches in patients with CDH are usually a mix of migraines and tension headaches. Medication overuse, especially of narcotics, caffeine-containing medications, barbiturates, and triptans, plays an important role in the development of CDH. Psychiatric factors including depression, personality disorders, and malingering are other important contributors. Unfortunately, treating CDH is extremely challenging, and any approach which I offer is better in theory than in practice. First, limit habit-forming analgesics as much as possible, as these only worsen symptoms over time. Use NSAIDs or, if absolutely required, longer-acting narcotics such as methadone or fentanyl for pain relief. Periodic lidocaine or ketamine infusions may also help. Although changing migraine and tension headache prophylactic regimens is usually of limited benefit, do not discard it as a futile approach. The CGRP antagonists may

be useful. Alternative therapies including biofeedback, acupuncture, and massage are effective for some patients. Finally, it is essential to address any important psychosocial factors such as depression, domestic abuse, and malingering. Although curing CDH is challenging and sometimes unobtainable, a multidisciplinary approach may help to restore the patient back to a reasonable functional level.

Headache in Pregnancy

Pregnant women may develop headaches which range in severity from entirely benign to malignant and life-threatening. Uncommon but dangerous causes of headache related to pregnancy include cerebral venous sinus thrombosis (see above), eclampsia (Chap. 20), and pituitary apoplexy (see above). Post-LP headaches (see above) may occur after epidural anesthesia. As a rule of thumb, any pregnant woman without a prior history of headaches should undergo MRI of the brain, especially if the headaches are associated with neurologic findings. The two most common headache types in pregnancy are migraines (which tend to improve in frequency and severity during pregnancy) and tension headaches (which often worsen during pregnancy). In general, it is best to avoid medications as much as possible during pregnancy, and there should be a frank risk-benefit discussion concerning all medications with the patient. Acetaminophen (650–1000 mg) and local ice pack application are the most benign treatments and should be tried first. For women who do not respond to these conservative approaches, use low doses of opioids or short courses of NSAIDs. Avoid NSAIDs in the late part of the third trimester, as they may lead to premature closure of the ductus arteriosus. Avoid triptans and dihydroergotamine altogether, as these medications may cause placental vasoconstriction. Magnesium and riboflavin are the safest options for migraine prophylaxis during pregnancy. Consider propranolol, amitriptyline, or nortriptyline if these are ineffective.

Facial Pain

Trigeminal Neuralgia

Trigeminal neuralgia, as its name suggests, is characterized by pain in the distribution of the trigeminal nerve, most commonly in its maxillary and mandibular divisions and rarely in the ophthalmic division. Patients describe sudden attacks of intense burning or electrical pain that shoot into the face and last for a few seconds at a time. In between the attacks of neuralgia, patients may note a residual aching pain in the affected trigeminal distribution. Almost all patients have multiple attacks per day. Patients with trigeminal neuralgia are characteristically able to trigger their pain by touching the cheek or jaw, shaving, brushing their teeth, or eating.

Classical trigeminal neuralgia is caused by microvascular compression of the trigeminal nerve as it enters the pons. Secondary trigeminal neuralgia occurs when a nonvascular lesion such as a mass lesion or demyelination in the brainstem affects

the nerve and is often accompanied by a reduction or loss of sensation in a trigeminal distribution. All patients with trigeminal neuralgia should undergo MRI of the brain with thin cuts through the brainstem and along the course of the trigeminal nerve to investigate for a responsible lesion.

Anticonvulsants and antidepressants are the mainstays of medical treatment for trigeminal neuralgia. The agent of first choice is carbamazepine, typically started at a dose of 200 mg bid and increased up to 600 mg bid as needed. Other options include:

- Baclofen 10 mg tid titrated up to 20 mg tid
- Gabapentin 300 mg tid titrated up to 1200 mg tid
- Oxcarbazepine 300 mg bid titrated up to 900 mg bid
- Phenytoin 100 mg tid
- Pregabalin 75 mg bid titrated up to 300 mg bid

Because trigeminal neuralgia pain is intense and disabling (it may provoke suicidal ideation in rare cases), it is important to switch medications quickly if it does not appear that the first agent chosen is working. Do not hesitate to prescribe narcotics in the acute stage of trigeminal neuralgia.

Misoprostol (200 μg tid) may be considered in patients with trigeminal neuralgia due to multiple sclerosis [28].

Unfortunately, some patients do not respond to medical treatment. Consider stereotactic radiosurgery for patients with refractory symptoms. The appropriate choice and optimal timing of referral for this procedure is not clear [29]. My practice is to refer patients after unsuccessful trials of two first-line medications. Microvascular decompression is reserved for patients with persistent symptoms after undergoing radiosurgery. For patients who fail to respond to even microvascular decompression, peripheral neurectomy of the affected branch of the trigeminal nerve is an option of last resort, as it results in permanent facial numbness and may do little to improve symptoms.

Glossopharyngeal Neuralgia

Glossopharyngeal neuralgia is characterized by lancinating pain affecting the larynx, tonsil, tongue, and ear. Pain is typically triggered by chewing, swallowing, touching the ear, or yawning. Physical examination is usually normal, although palatal elevation and the gag reflex may be reduced ipsilateral to the lesion. All patients with glossopharyngeal neuralgia and examination signs of glossopharyngeal nerve dysfunction should undergo an MRI of the brain and neck with thin cuts through the brainstem to look for a responsible lesion in the lower pons or medulla, a mass lesion at the jugular foramen, or compression of the nerve in its course through the neck. The medical treatment of glossopharyngeal neuralgia is similar to that which is employed for trigeminal neuralgia. In most cases, neurosurgical evaluation is not required, but microvascular decompression of the glossopharyngeal nerve may help patients with refractory symptoms.

Intermedius Neuralgia

This rare disorder characterized by a stabbing pain that emanates from the inner ear is due to ephaptic transmission from the intermedius nerve, which runs between the seventh and eighth cranial nerves. Provided that no structural explanation is identified, intermedius neuralgia can be treated in a similar fashion to trigeminal neuralgia.

Sinus Headache

Inflammation of the nasal mucosa and sinuses commonly produces a sensation of facial pressure rather than frank pain. Patients with sinusitis describe fullness or aching in the forehead, cheeks, the bridge of the nose, and the upper jaw. Nasal discharge and blockage usually accompany the pressure. Finding tenderness to percussion of the sinuses or maxilla help to make the diagnosis, but confirmatory CT scan of the sinuses is required in unclear cases. Be cautious about attributing headaches or facial pain to mild sinus abnormalities on a head CT or MRI, as radiographic evidence of sinus congestion is frequent in otherwise healthy people, and many patients who are diagnosed with sinus headaches actually have a different source for headaches. Treat sinus headache patients with decongestants. Refer patients with refractory symptoms to an otorhinolaryngologist.

Temporomandibular Joint (TMJ) Disease

TMJ disease is a relatively common myofascial pain syndrome which consists of preauricular aching, limitation of mandibular motion, and crepitus with jaw movement. The exact etiology of the syndrome is unclear but includes both biological and psychosocial factors [30]. The pain is usually unilateral and is often present with or without chewing. Jaw locking is a common symptom. Occasionally, TMJ disease presents to a neurologist as a primary headache localized to the temple, vertex, or occiput. Pain with palpation of the TMJ and crepitus with jaw movement suggest the diagnosis. Panoramic radiographs are the most useful screening study. Heat, muscle relaxants, nonsteroidal anti-inflammatory drugs, and tricyclic antidepressants may improve symptoms. Refer patients with refractory disease to a dentist with specific interest in TMJ disease for fitting of an intraoral occlusive orthotic device (bite plate) or possibly for surgical correction of the problem.

Herpes Zoster and Post-herpetic Neuralgia

Varicella zoster may lie dormant in the trigeminal sensory ganglia for years, being reactivated by stress or illness. Symptoms typically begin with paresthesias or lancinating pains which are followed in a few days by a vesicular rash in one of the divisions of the trigeminal nerve. The rash may be painful, and after it heals, the patient may continue to complain of exquisite pain in the affected dermatome

(post-herpetic neuralgia). Treat herpes zoster with valacyclovir (1000 mg tid for 7 days). Use gabapentin (300–1200 mg tid) for acute pain or post-herpetic neuralgia. Some patients benefit from capsaicin cream, which should be used cautiously (or not at all) in patients with herpes zoster ophthalmicus.

Atypical Facial Pain Syndrome

Atypical facial pain is characterized by unilateral or bilateral facial pain which usually has a dull, aching quality. Patients often undergo evaluation and treatment for years before the diagnosis is made. The etiology of atypical facial pain is unclear, but the condition often overlaps with myofascial pain syndromes and fibromyalgia. Atypical facial pain should be considered only after other sources of facial pain are excluded by careful clinical history, examination, and neuroimaging studies. The mainstays of treatment include selective serotonin reuptake inhibitors and tricyclic agents. Patients with atypical facial pain who are evaluated by neurologists frequently have refractory symptoms, and a multidisciplinary approach including alternative therapies is often required.

Primary Headache Disorders Presenting with Facial Pain

Tension, migraine, and cluster headaches may present as facial pain rather than as headache. The diagnosis may be straightforward when the typical headaches accompany the facial pain. A trial of empiric treatment is often the only way to establish that a primary headache disorder is the source of facial pain.

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Seizures and Epilepsy

20

The First-Time Seizure

An epileptic seizure is a transient occurrence of neurologic signs and/or symptoms due to abnormal, excessive, synchronous neuronal activity in the brain [1]. Seizures are a very common neurological problem, and the first-time seizure is a frequent reason for neurological consultation. An organized approach when evaluating a first-time seizure consists of the following steps:

1. Get the best account of the seizure manifestation (ictal semiology) from a first-hand observer.
2. Determine whether the event was actually a seizure.
3. If it was a seizure, determine whether it was the first one.
4. Define the etiology of the seizure.
5. Determine whether treatment is needed and, if so, what agents are appropriate.

Ictal Semiology

Generalized Tonic-Clonic Seizures

The generalized tonic-clonic seizure (GTCS) is the most easily recognized type of seizure and the one that most frequently leads to emergency room and inpatient consultations. Because a GTCS is usually quite alarming, eyewitness accounts are often unreliable, even when provided by a physician or nurse. Sometimes, the only available information is that the patient passed out and shook. Although there is considerable heterogeneity, a GTCS lasts for an average of about a minute and consists of some or all of the following phases [2]:

1. Focal seizure. A GTCS may be primary generalized, in which case it is unassociated with a focal seizure, or it may arise from a focal seizure in a process known as secondary generalization. If this focal seizure is a simple focal seizure (see

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below), the patient may remember it later. However, patients will not be able to remember GTCS that are generalized from onset or which develop from focal seizures with loss of awareness.
2. Onset of generalization. After the focal seizure ends, secondary generalization is usually heralded by a forced head movement to one side (versive movement) or by a brief vocalization.
3. Pre-tonic-clonic phase. In approximately half of patients, generalization begins with irregular, asymmetric clonic jerking of the extremities.
4. Tonic phase. This is a generalized stiffening caused by a sustained contraction of all the muscles in the body. It may be accompanied by some clonic jerking.
5. Tremulous phase. This phase is characterized by fast muscle shaking.
6. Clonic phase. This is the final phase of the seizure itself, characterized by slower muscle jerking which eventually decreases in frequency before stopping.
7. Postictal state. After a GTCS, the patient lies limp, in a deep sleep. After several minutes, they awaken and become confused, possibly with a headache and muscle pain from the seizure.

An observer is never capable of providing this level of detail when describing a seizure, and even careful videotaped analysis seldom leads to this type of description.

Focal Seizures

Focal seizures begin in a focal area of the brain and are the most common seizure types in adults. Because they may arise from any area of the cerebral cortex, focal seizures produce a vast array of motor, sensory, perceptual, and behavioral manifestations. Focal seizures are divided into seizures in which awareness is preserved, and which therefore can be described by the patient, and those in which there is impaired awareness (formerly known as complex partial seizures).

Focal Seizures with Preserved Awareness

Motor Seizures

Focal seizures arising from motor cortex may take the form of forced head deviation to one side, speech arrest or vocalizations, stereotyped limb or facial movements such as twitching or jerking, or coordinated, almost purposeful-appearing movements. When a motor seizure remains restricted to one area of the cortex, it produces only a single manifestation. A Jacksonian march occurs when there is sequential spread of the seizure activity through the motor homunculus: the seizure may start in the face and then spread quickly to the hand, arm, and leg. Focal motor seizures may be followed by Todd paralysis in which muscle weakness lasts for several minutes to hours.

Sensory Seizures

Focal seizures may affect any sensory modality. Common sensory auras include visual (seeing spots, stars, or bright lights), auditory (ringing, buzzing, or musical sounds), somesthetic (tingling, numbness, or electrical sensations), olfactory (the

smell of burning rubber or other foul odors), gustatory (acidic, bitter, or sweet tastes), vestibular (vertigo), or epigastric (the sensation of rising in the abdomen, descending a roller coaster, or having butterflies in the stomach). Auras that involve primary sensory cortex are generally unformed and primitive, whereas those that involve higher-level association cortex or mesial temporal structures are more detailed.

Cognitive and Emotional Seizures

Focal seizures, particularly those that originate from the temporal lobe, may manifest as cognitive or emotional phenomena. *Dejà vu* is the sensation of visual familiarity, while *dejà entendu* is the sensation of auditory familiarity. *Jamais vu* and *jamais entendu* are feelings of unfamiliarity in the visual and auditory realms, respectively. Patients with focal temporal seizures may also describe a dreamlike or disconnected state, or a sense that they are watching themselves (autoscopy). Depersonalization, fear, pleasure, religious ecstasy, and forced thinking are also well-described psychic auras generated by the temporal lobes.

Focal Seizures with Impaired Awareness

Focal seizures may lead to impaired awareness. These can be accompanied by automatic, repetitive, stereotyped behaviors known as automatisms. Automatisms arising from the temporal lobe tend to be simple and include lip smacking, chewing, swallowing, grasping, fumbling, blinking, and eye fluttering. Automatisms arising from the frontal lobe are usually more complex and often appear purposeful. Orbitofrontal automatisms may have bizarre characteristics including bicycling movements of the legs, pelvic thrusting, and mimicry of sexual activity.

Absence Seizures

Absence seizures begin in childhood or adolescence. In some cases, they are misdiagnosed as focal seizures, and the correct diagnosis is not made until adulthood. Typical absence seizures last for just a few seconds and are characterized by unresponsiveness, a fixed, blank stare, eye fluttering, and facial twitching [3]. Accompanying seizure manifestations may include increases or decreases in postural tone, brief clonic movements, and automatisms that resemble those of patients with focal seizures. Patients with absence seizures may or may not be aware of an attack and resume pre-ictal activities as soon as the seizure is completed.

Myoclonic Seizures

Myoclonus is a sudden, involuntary, brief jerk of a muscle or group of muscles which is discussed in further detail in Chap. 12. Although myoclonic seizures tend to occur in children, they may also be first recognized in adolescents or young adults as part of juvenile myoclonic epilepsy (see below). Uncommon degenerative conditions associated with myoclonic seizures (progressive myoclonic epilepsies) include adult-onset neuronal ceroid lipofuscinosis, Lafora body disease, sialidosis, Unverricht-Lundborg disease, and myoclonic epilepsy with ragged red fibers (MERRF).

Atonic Seizures

Atonic seizures are sudden drop attacks in which the patient loses tone and falls to the ground. They are associated with mental retardation and the Lennox-Gastaut syndrome. Atonic seizures are frequently included in the differential diagnosis of falls and syncope but should be omitted because they *do not occur in cognitively normal adults*.

The Differential Diagnosis of Seizures

Syncope

The condition that most commonly is confused with GTCS is syncope, a sudden, brief loss of consciousness that results from reduced cerebral blood flow (Chap. 9). It is usually preceded by lightheadedness, diaphoresis, and anxiety. Syncope may be accompanied by multifocal jerking movements in 50–90% of patients [4]. These myoclonic movements usually last for only 3–10 seconds and are brainstem release phenomena rather than abnormal, synchronous cortical discharges. After syncope, patients regain consciousness and coherence within a few seconds, often in response to elevation of their feet, which restores cerebral blood flow. Patients with GTCS, on the other hand, require minutes to hours after an event to recover coherence. Features that help to differentiate between seizures and syncope are found in Table 20.1. The most reliable of these is the presence of a postictal state, which strongly favors seizure.

Migraine and Transient Ischemic Attack

Simple and complex focal seizures have a broad differential diagnosis. Among neurological conditions, the two that are the most difficult to distinguish from focal seizures are migraine aura and transient ischemic attack (TIA). Prior history of migraine or risk factors for cerebrovascular disease may help to suggest these conditions. In the absence of a relevant past medical history, the time course over which symptoms develop is the most useful distinguishing piece of information: with some exceptions, seizures develop over seconds, migraine auras spread over several minutes, and TIA symptoms are maximal at onset. One particular form of TIA that is very easy to confuse with a seizure is the limb-shaking TIA in which brief, irregular, tremulous movements of the arm or arm and leg occur as a result of hypoperfusion in a patient with carotid artery stenosis [5].

Table 20.1 Factors which help differentiate between seizure and syncope

Seizure	Syncope
Tongue biting	Lightheadedness
Urinary incontinence	History of cardiovascular disease
Head turning	Chest pain
Posturing	Diaphoresis
Amnesia for the event	Facial flushing
Postictal confusion	
Déjà vu/Jamais vu	

Movement Disorders

Motor seizures may be confused with movement disorders, especially myoclonus and hemiballismus (Chap. 12). With the rare exception of epilepsia partialis continua in which focal seizures occur continuously, most seziures are discrete events that are separated in time by hours, days or months. Most movement disorders tend to be relatively continuous activities. For example, intermittent flinging of the arm lasting for days on end is more likely to be the movement disorder hemiballismus than a focal motor seizure.

Sensory Symptoms

The differential diagnosis of sensory seizures depends on the affected sensory modality. In all cases, consider dysfunction of the sensory end organ (e.g., the eye in patients with visual symptoms) before concluding that the problem is coming from the brain. Patients with olfactory or gustatory phenomena, for example, may have primary otorhinolaryngologic disorders or may be taking a medication that leads to their abnormal smells or tastes. Auditory hallucinations usually occur in the context of psychotic disorders. Somatosensory deficits secondary to seizures should not be fixed, unlike disorders of the peripheral nervous system or spinal cord such as radiculopathy, compression neuropathy, and multiple sclerosis.

Psychiatric Disorders

Psychic and affective focal seizures must be differentiated from psychosis and depression, a task which may require the assistance of a psychiatrist. Malingering and conversion disorders (*see below*) are relevant considerations in all patients with paroxysmal disorders. Despite careful probing, an EEG recorded during an event is often the only reliable way to determine whether a behavior or perception is a seizure.

Narcolepsy

Narcolepsy is a disorder characterized by the tetrad of excessive daytime sleepiness, cataplexy (sudden loss of muscle tone, often precipitated by laughter or other emotional states), hypnagogic hallucinations (which occur upon going to sleep), and sleep paralysis. Although differentiating narcolepsy from seizures is almost always straightforward, rare patients with cataplexy as their first or only symptom may be referred to a neurologist for seizure evaluation. The diagnosis should be obvious from the history alone. A multiple sleep latency test (MSLT) helps to establish the diagnosis in unclear cases. Treatment should include referral to a sleep specialist. Modafinil (200 mg qd-bid) and methylphenidate (10 mg bid) are the most commonly used treatments for the excessive daytime sleepiness of narcolepsy, while REM-suppressing medications such as extended-release venlafaxine (75–150 mg qd) and fluoxetine (20–40 mg) are most often used for cataplexy. Sodium oxybate (starting at 3 g twice per night) is used for patients with refractory cataplexy.

Was This Really the First Seizure?

Determining whether a seizure was a patient's first one is essential to guide further evaluation and treatment. When asking a patient about prior seizures, keep in mind that a person who has a GTCS will remember only the postictal state and not the seizure itself. Ask the patient, therefore, if they have ever awoken with a confused feeling, unexplained injuries, tongue lacerations, or loss of urine. Because most people are not familiar with seizures other than GTCS, it is important to inquire directly about specific focal seizure phenomena described above, staring spells indicative of absence seizures, and myoclonic seizures.

Determining Seizure Etiology

Because a seizure is a symptom of brain dysfunction rather than a disease unto itself, determining its underlying cause is an essential, but often overlooked, part of the evaluation. Seizure etiologies may be divided broadly into two groups: those that are caused by identifiable and often reversible metabolic or structural processes and those that have no identifiable cause. In the search for a seizure etiology, all patients require a careful and complete medical and neurological history. This includes inquiring about habits such as substance abuse and family history of seizures and other neurologic disorders.

Laboratory Testing

Laboratory testing for a first-time seizure patient is very similar to that which is performed for the confused patient (Chap. 1) and should include a complete blood count; chemistry studies with calcium, magnesium, and phosphorous levels; liver function tests; toxicology screen; and urinalysis. Minor laboratory abnormalities, while common, are usually not the proximate cause of the seizure. Lumbar puncture should be considered for patients with fever, a history of immunosuppression, or other reasons to suspect encephalitis or an autoimmune seizure etiology. Although GTCS by themselves may cause CSF pleocytosis, the number of cells rarely exceeds 1–2 per mm^3, and any value exceeding 10 cells/mm^3 should prompt evaluation and empiric treatment for meningitis or encephalitis [6].

Neuroimaging

All patients with a first-time seizure should undergo a neuroimaging study: approximately 10–15% of patients will have an abnormal finding that could account for their seizure [7]. In the acute setting, non-contrast head CT is sufficient to evaluate for structural lesions that require urgent attention such as brain hemorrhage, tumor, and abscess. Slowly growing tumors with mass effect or edema, encephalitis, and ischemic stroke are seizure etiologies that may not be detected by CT. MRI with seizure-specific protocols should be obtained shortly after the first seizure for patients without an obvious seizure etiology.

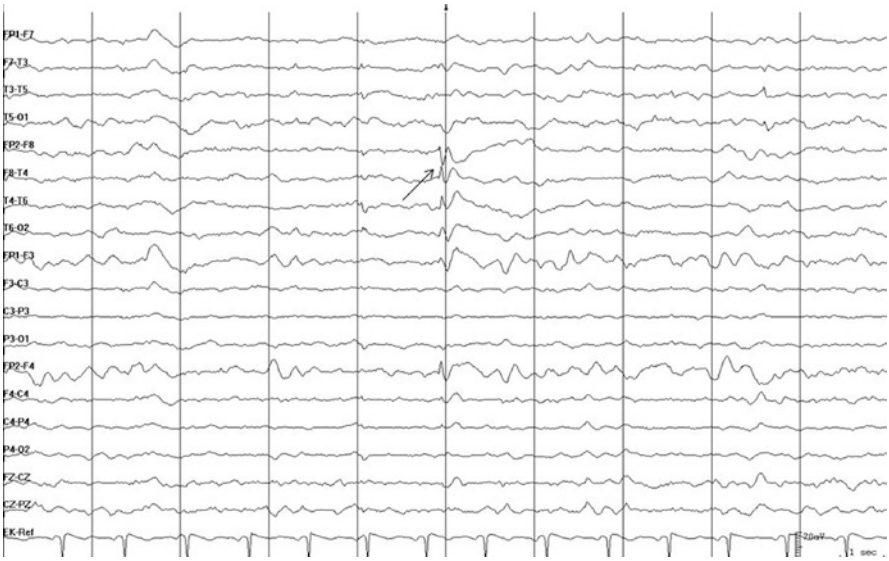

Fig. 20.1 Interictal EEG in a patient with a recent partial-onset seizure. Note the sharp wave with phase reversal at the F8 lead (arrow), placing the seizure focus in the right frontal lobe. (Image courtesy of Dr. Julie Roth)

Electroencephalography (EEG)

EEG is valuable diagnostic tool in evaluating a patient with a first-time seizure: it helps to differentiate epileptic seizures from conditions that mimic them and to classify seizure types and tailor therapy. Most patients with a first-time seizure will have their EEG between seizures rather than during a seizure. Abnormal interictal epileptiform discharges (Figs. 20.1 and 20.2) are present in approximately 30% of these patients, but also in approximately 2% of normal subjects [7, 8]. The yield of EEG increases with sleep deprivation, by performing multiple studies and by performing the study in close proximity to the seizure [9].

Specific Seizure and Epilepsy Etiologies

Electrolyte Abnormalities

Many electrolyte abnormalities are minor, and not the direct cause of seizures. Rapid changes in electrolyte levels are often more important than the absolute levels, but the following are rough guidelines to electrolyte levels that might be the explanation for new or worsening seizures:

- Hyponatremia <120 mEq/L
- Hypocalcemia <6 mg/dL
- Hypomagnesemia <0.8 mg/dL
- Hypophosphatemia <1 mg/dL

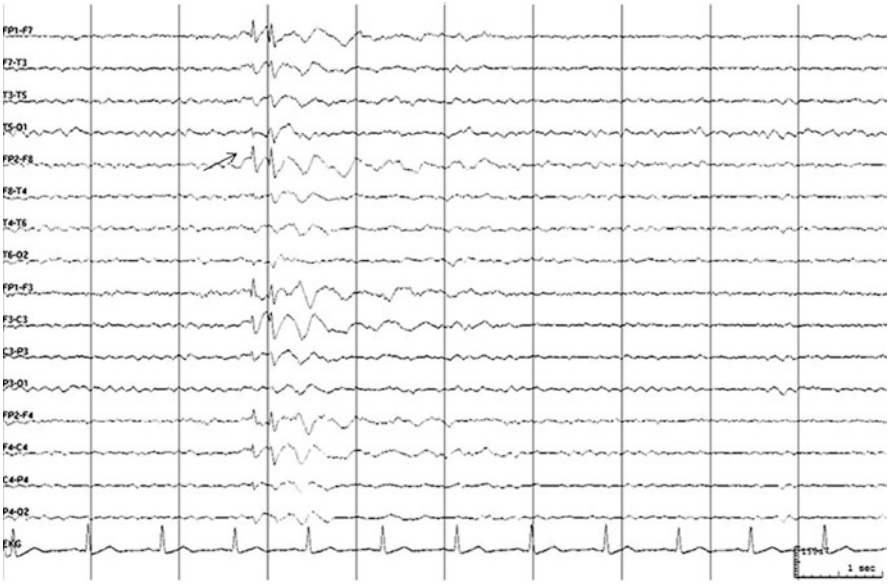

Fig. 20.2 Interictal EEG in a patient with primary generalized epilepsy. Note the generalized sharp discharges followed by slow waves. (Image courtesy of Dr. Julie Roth)

Careful correction of these electrolyte abnormalities should reduce the chances of seizure recurrence.

Uremia and Dialysis Disequilibrium

Both acute and chronic renal failure lead to the accumulation of toxic metabolites and uremic encephalopathy (Chap. 1) [10]. Patients with uremic encephalopathy may have both generalized and focal seizures, although GTCS are more common. Uremic seizures are often accompanied by myoclonus. There is no single blood urea nitrogen, creatinine, or glomerular filtration rate that predicts seizures: the diagnosis must be made on clinical judgment. Dialysis is the definitive treatment of seizures secondary to uremia, but some patients may require antiepileptic drugs (AEDs) as additional therapy. Patients undergoing dialysis are at risk for dialysis disequilibrium, which may include encephalopathy, seizures, blurred vision, loss of consciousness, or coma. Dialysis disequilibrium is best avoided by performing the dialysis sessions gently, improves with corrective measures, but may recur.

Glucose Imbalance

Because glucose is the brain's primary energy source, hypoglycemia is a substrate for neurologic dysfunction including seizures. The glucose level at which seizures occur varies from patient to patient: in diabetics, seizures may occur at relatively higher glucose levels than in healthy patients, as diabetics develop long-term tolerance to high blood sugar levels. Nonketotic hyperglycemia may also precipitate seizures (sometimes taking the form of continuous focal seizures, i.e., epilepsia

partialis continua), but ketotic hyperglycemia is not a direct cause of seizures because ketosis raises the seizure threshold.

Hepatic Encephalopathy

Hepatic encephalopathy and associated seizures are discussed in greater detail in Chap. 1.

Posttraumatic Seizures

Although figures vary from study to study, a rough estimate of seizure risk is 5% for patients with closed head injuries and 50% for those with penetrating head injuries [11]. Not surprisingly, the seizure risk is greater in patients with severe injuries than in those with mild injuries. Posttraumatic seizures may be divided into early seizures, which occur within 1 week of head injury, and late seizures which occur more than 1 week after head injury. Early seizures are usually GTCS and may take the form of status epilepticus. It is important to treat these seizures as they occur, but because early seizures are not necessarily associated with a higher risk for developing posttraumatic epilepsy, prophylactic AEDs should not be prescribed routinely for these patients [12, 13]. Patients with late seizures are at increased risk for developing epilepsy, even many years after the injury, and should be treated with AEDs [13].

Alcohol Withdrawal

Alcohol withdrawal may lead to seizures, which are almost exclusively GTCS. These seizures occur within 72 hours of the last drink, with a peak between 6 and 24 hours after alcohol discontinuation [14]. Patients withdrawing from alcohol should undergo careful evaluation as they often have accompanying head trauma, electrolyte abnormalities, or meningitis that may precipitate seizures independently. Although alcohol withdrawal seizures do not require AEDs acutely or chronically, benzodiazepines prescribed for other symptoms of withdrawal are useful in the short term.

Other Medications and Toxins

A variety of medications including certain antidepressants, antipsychotics, stimulants, anesthetics, and antibiotics may precipitate seizures. It is good practice to review the manufacturer's prescribing information to determine whether a new medication played a role in lowering a patient's seizure threshold and then to discontinue the offending medication if possible. Intoxication with drugs of abuse (particularly stimulants and hallucinogens) and withdrawal from benzodiazepines also causes seizures.

Meningitis and Encephalitis

Patients with meningitis and encephalitis are at risk for seizures. Consider performing lumbar puncture in patients with new seizures and a fever of undetermined source after a space-occupying lesion is excluded by head CT. Chapter 1 contains a more detailed discussion of meningitis and encephalitis.

Neurocysticercosis

Infection of the brain parenchyma by the parasite *Taenia solium* is the most common cause of seizures in many Latin American and African countries. Cysts of all stages, including calcified cysts, may precipitate seizures. Other manifestations of neurocysticercosis include headaches, focal neurologic disturbances, and, in some cases, hydrocephalus due to ventricular obstruction. The diagnosis of neurocysticercosis is usually established radiographically, and in most patients, CT scan is sufficient. Enzyme-linked immunoelectrotransfer blot assay is useful when the diagnosis is in question. Treat patients with seizures and enhancing cysts with a combination of AEDs and albendazole (400 mg bid) and prednisone (60–80 kg qd) under the guidance of an infectious disease specialist [15]. Antiepileptic drugs need to be administered until the responsible lesions have resolved.

Neoplasms

Although precise numbers are difficult to establish, between 3% and 15% of epilepsy is due to brain tumors, with patients who develop seizures in middle age having the greatest probability of a neoplastic etiology [16]. Approximately 35% of patients with brain tumors will eventually have a seizure [17]. The relative likelihood is greatest with low-grade gliomas, then with meningiomas, followed by high-grade gliomas, and least for metastatic tumors [17]. Cortically based tumors are more likely to lead to seizures. The study of choice to evaluate for brain tumor is MRI with and without contrast (Chap. 23). When evaluating patients with known cancer who develop seizures, it is important to keep in mind sources of seizures other than metastasis, including meningitis from immunosuppression, paraneoplastic limbic encephalitis, radiation necrosis, scarring from surgical resection sites, and hemorrhage due to coagulopathy. Levetiracetam is often the agent of choice for patients with brain tumors as it does not interact with commonly prescribed chemotherapeutic agents. Despite common practice, AED prophylaxis is not required for all patients with brain tumors, unless there is a seizure history [18].

Stroke

Cerebrovascular disease is the most common identifiable source of seizures and epilepsy in adults and is especially common in the elderly. One prospective study showed that approximately 9% of patients with a stroke will have a seizure, usually within 24 hours of the stroke [19]. Both ischemic and hemorrhagic strokes predispose patients to seizures. Most seizures secondary to hemorrhagic stroke occur in the first few weeks after the stroke, whereas the risk of seizures secondary to ischemic stroke is more likely to persist for months or even years after the stroke [20, 21]. Seizures that occur months or years after a stroke are more likely to require AED treatment than those that occur in the immediate post-stroke period [20]. When evaluating patients with a prior history of stroke who present with a new seizure, it is important to consider other etiologies rather than to assume that the stroke is the explanation.

Anoxic Brain Injury

Approximately 30% of patients who have sustained cardiac arrest develop seizures [22]. Status epilepticus and myoclonic seizures generally portend a poor outcome,

particularly when accompanied by CT or MRI findings of diffuse anoxia. Nonetheless, patients with both status epilepticus and myoclonic seizures may have good outcomes, and these seizures should be treated unless medical care is withdrawn due to overall poor prognosis.

Arteriovenous Malformations

Arteriovenous malformations may cause a variety of symptoms including intracranial hemorrhage, stroke, and seizure. They are discussed further in Chap. 23.

Neurodegenerative Diseases

Up to 15% of patients with Alzheimer disease (AD) may have seizures, usually GTCS [23]. It is not clear how frequently the seizures are the direct consequence of AD, but in many patients with seizures, AD may be the only identifiable pathology. Other neurodegenerative diseases including Creutzfeldt-Jakob disease and frontotemporal dementia are also associated with seizures.

Juvenile Myoclonic Epilepsy (JME)

This disorder usually begins in adolescence but may go undiagnosed until early adulthood. Many patients start with absence seizures in youth that are misinterpreted as attention deficit hyperactivity disorder (ADHD) symptoms. Myoclonic jerks in the arms, usually after awakening in the morning, are the most common initial feature specific to the disease. GTCS develop later in the course and are often the events that bring the patient to clinical attention. In many cases, the features of the syndrome may be identified only retrospectively by careful history. Interictal EEG characteristically shows 4–6 Hz spike-wave complexes (Fig. 20.3). Although it is considered a benign form of epilepsy, most patients with JME require lifelong treatment with AEDs to prevent seizure recurrence. Valproate, levetiracetam, and lamotrigine are the most effective medications for the treatment of JME.

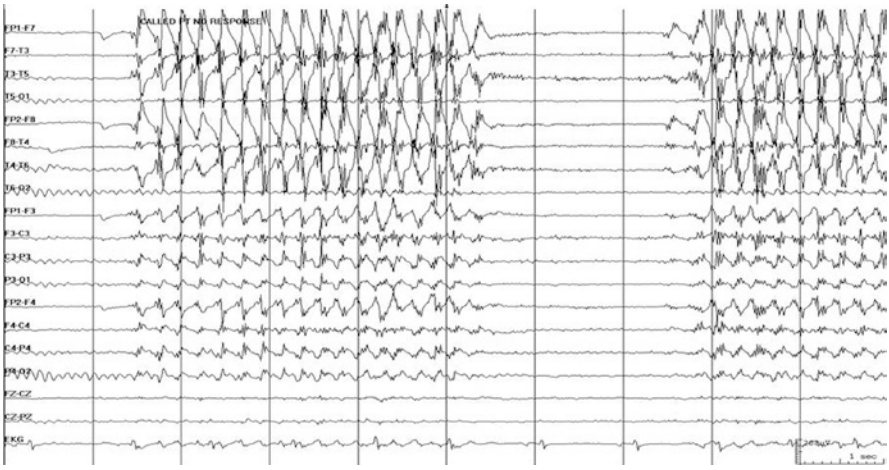

Fig. 20.3 Fast (4–5 Hz), generalized polyspike-wave complexes seen in patient with juvenile myoclonic epilepsy. (Image courtesy of Dr. Julie Roth)

Eclampsia

Preeclampsia is a condition specific to pregnancy consisting of the triad of hypertension, proteinuria, and edema. It may occur at any time between week 20 of gestation and 6 weeks postpartum. The only cure for preeclampsia is delivery. Eclampsia is the occurrence of seizures in a woman with preeclampsia. The seizures are usually GTCS, may be severe, and may threaten both mother and baby. Magnesium sulfate is the preferred therapy to prevent preeclampsia from developing into eclampsia and to prevent seizure recurrence in patients who have already had an eclamptic seizure [24–26]. Treat women with severe preeclampsia or eclamptic seizures with 6 g intravenous magnesium sulfate followed by an intravenous drip of 2–3 g/hr. Because high levels of magnesium may cause respiratory depression, neuromuscular transmission failure, or kidney dysfunction, it is important to hold the infusion for any decline in respiratory rate, loss of deep tendon reflexes, or decrease in urinary output.

Catamenial Epilepsy

Many women with epilepsy experience greater seizure frequency or seizures limited to the perimenstrual or periovulatory period. This is known as catamenial epilepsy. It is important that the patient keep a seizure diary to establish this pattern. In addition to the typical first-line AEDs, women with catamenial epilepsy may benefit from acetazolamide 250–500 mg bid or clobazam 20–30 mg qd starting 2–3 days prior to the typical monthly seizure exacerbation [27, 28].

Autoimmune and Paraneoplastic Epilepsy

Although uncommon, autoimmune disorders may produce encephalitis and seizures. Refractory seizures at the onset of epilepsy are suggestive of an autoimmune or paraneoplastic etiology. Connective tissue disorders such as systemic lupus erythematosus and the antiphospholipid antibody syndrome may cause epilepsy. Important autoantibodies associated with epilepsy include those to the NMDA receptor, GABA-A, GABA-B, AMPA, CRMP5, GAG, LGI-1, and CASPR2 (Chap. 1).

Seizures of Unknown Origin

The majority of adults with new-onset seizures have no specific identifiable etiology [16]. These patients presumably have an underlying genetic or unidentified environmental cause for their seizures.

Treatment of the First-Time Seizure

Provoked Seizures

Provoked seizures are those that are caused by a specific, identifiable abnormality and which do not recur when that abnormality is corrected. Common causes of provoked seizures include electrolyte disturbances and alcohol withdrawal.

Provoked seizures should not be treated with long-term AEDs as they have a low likelihood of recurrence and definitive treatment is correction of the responsible seizure etiology.

The Chance of Seizure Recurrence

Choosing to prescribe AEDs for a patient after a single seizure is often a difficult decision, and each patient must be approached individually. Understanding the overall risk of seizure recurrence is helpful in making the decision to start AEDs. For an adult with a single unprovoked seizure, the 2-year risk of seizure recurrence is approximately 50% [29, 30]. The probability of seizure recurrence increases to 60–70% if there is a history of prior neurologic injury, developmental abnormalities, abnormal neuroimaging studies, or an EEG with epileptiform abnormalities [30]. Although a 50% risk of seizure recurrence would seem to warrant AED therapy, the side effects of taking these AEDs must be weighed against their protective effects. Historically, AEDs were not prescribed for patients after a single seizure, but the availability of newer, less toxic options has made starting medication after a first seizure a more common practice. Ultimately, the decision to start AEDs must be made in conjunction with the patient and should take their risk tolerance and lifestyle into account. For example, it is reasonable to start an AED in a patient with a first seizure if their livelihood depends on the ability to drive. An older person with many comorbidities and high chances of medication interactions or other cognitive side effects might not be a good candidate for an AED after a first seizure.

After a second seizure, the 2-year risk for further seizures increases to approximately 70% [29]. AEDs are almost always prescribed for patients after a second unprovoked seizure. Possible exceptions to this rule include patients with non-disabling nocturnal seizures or elderly nursing home residents who are at high risk for side effects from AEDs.

Choosing an AED

In most cases, there is little difference in efficacy among the various AEDs, and the choice of agent is usually based on the anticipated side effects, background medical history, potential for interaction with other medications, cost, and speed with which the medication can be titrated to effective levels. There is no single AED that can be labeled as the “best” or the “first choice” for all patients. Table 20.2, however, contains a summary of common applications in which certain AEDs may be preferred based on expert consensus and personal experience, while Table 20.3 contains a summary of the dosing and side effects of commonly used AEDs [31].

AEDs in Patients with Renal Dysfunction

Many hospitalized or otherwise chronically ill patients have renal dysfunction that complicates selection of AEDs. Hemodialysis may remove AEDs entirely, partially, or not at all. Table 20.4 contains a summary of dose adjustments for common AEDs in patients with renal dysfunction and hemodialysis.

Table 20.2 Anticonvulsants and specific applications

Application	Anticonvulsants of choice
Focal seizures and secondarily Generalized seizures	Phenytoin, carbamazepine, Oxcarbazepine, levetiracetam, lamotrigine, valproate
Primary generalized tonic-clonic seizures	Valproate, lamotrigine
Absence seizures	Valproate, ethosuximide
Juvenile myoclonic epilepsy	Valproate, levetiracetam
Need to start anticonvulsant quickly at goal dose	Phenytoin, levetiracetam
Patient taking multiple medications which would potentially interact with anticonvulsants	Levetiracetam, lacosamide
Medication expense is a concern	Phenytoin, carbamazepine, valproate
Pregnancy	Lamotrigine, levetiracetam (avoid valproate if possible)
Hepatic failure	Levetiracetam, topiramate, gabapentin
Renal failure	See Table 20.4

Table 20.3 Common anticonvulsants

Anticonvulsant name	Starting dose	Titration method	Initial goal dose	Typical therapeutic levels, μg/mL[a]	Side effects[a]
Phenobarbital	30 mg qd	Increase by 30 mg every 2 weeks	60–120 mg qd	10–40	Excessive sedation
Phenytoin	100 mg tid	See Box 20.1	See Box 20.1	10–20	Rash, pseudolymphoma, gingival hyperplasia, hirsutism, polyneuropathy, cerebellar degeneration
Carbamazepine	200 mg bid	Increase by 200 mg total every 3 days (autoinduction of metabolism may require readjustment after ~4 weeks)	200–400 mg bid	4–12	Rash including Stevens-Johnson syndrome, hyponatremia, agranulocytosis
Valproate	500 mg bid	Increase by 250 mg per dose each week	500–1000 mg bid	50–100	Tremor, thrombocytopenia, pancreatitis, hyperammonemia, weight gain, hair loss
Lamotrigine	25 mg qd	Increase by 25 mg each week (see Box 20.1)	100–200 mg bid	Not established	Rash including Stevens-Johnson syndrome
Gabapentin	300 mg qd	Increase by 300 mg total every 3 days	600–1200 mg tid	Not established	Minimal beyond sedation, dizziness, and ataxia
Topiramate	25 mg qd	Increase by 25 mg each week	100–200 mg bid	Not established	Weight loss, anomia, nephrolithiasis, acral paresthesias

Table 20.3 (continued)

Anticonvulsant name	Starting dose	Titration method	Initial goal dose	Typical therapeutic levels, μg/mL[a]	Side effects[a]
Oxcarbazepine	150 mg bid	Increase total dose by 300 mg each week	300–600 mg bid	Not established	Hyponatremia, rash including Stevens-Johnson syndrome
Levetiracetam	500 mg bid	Increase total dose by 500 mg each week	500–1500 mg bid	Not established	Irritability
Zonisamide	50 mg qd	Increase total dose by 50 mg each week	100–200 mg qd	Not established	Paresthesias, anorexia, kidney stones
Lacosamide	50 mg bid	Increase total dose by 50 mg each week	100–200 mg bid	Not established	Dizziness, PR interval prolongation
Rufinamide	400 mg qd	Increase by 400 mg qod	1600–3200 mg qd	Not established	QT interval shortening
Clobazam	5 mg bid	Increase by 5 mg bid each week	10–20 mg bid	Not established	Sedation, restlessness, excessive salivation
Eslicarbazepine	800 mg qd	Increase by 400 mg qd each week	800–1600 mg qd	Not established	Hyponatremia, rash
Brivaracetam	50 mg bid	Adjust to 25–100 mg bid within 1 week	25–100 mg bid	Not established	Irritability
Perampanel	2 mg qd	Increase by 2 mg qd each week	8–12 mg qd	Not established	Aggression, headache, blurred vision

[a]Side effects of all medications include dose-related sedation, dizziness, and ataxia

Table 20.4 Anticonvulsants in patients with renal dysfunction [52]

Anticonvulsant name	Adjustment in renal failure	Supplemental dose after hemodialysis?
Phenobarbital	No	Yes
Phenytoin	No	Yes
Carbamazepine	No	No
Valproate	Frequent monitoring	Yes
Topiramate	No	Yes
Lamotrigine	No	Yes
Gabapentin	CrCl 30–60 mL/min 300 mg bid; CrCl 10–30 mL/min 300 mg qd; CrCl <10 mL/min 300 mg qod	Yes
Oxcarbazepine	No	No
Levetiracetam	CrCl 50–80 mL/min 500–1000 mg bid; CrCl 30–50 mL/min 250–750 mg bid; CrCl <30 mL/min 250–500 mg bid	Yes
Zonisamide	Frequent monitoring	Yes
Lacosamide	Maximum dose 300 mg qd in severe renal failure	Yes
Rufinamide	No	No
Clobazam	No	No

CrCl creatinine clearance

Counseling After the First Seizure

Counseling after a first seizure is an important part of seizure management. Review seizure manifestations (especially for patients with focal seizures) and what to tell schools or workplaces about the seizures. It is also imperative to tell family members that they should not put a spoon or other objects into a patient's mouth during a seizure. It is a popular misconception that a person can swallow their own tongue during a seizure. This cannot happen, but they can choke on a foreign body such as a spoon. Instruct family members that the safest place for a patient during a GTCS is on the floor, placed on their side to prevent aspiration. Let family members know that any GTCS that lasts more than 5 minutes is potentially dangerous and requires immediate medical attention. Remind patients and their families to look at the clock as soon as a seizure begins, because seizure duration is often overestimated, and knowing an accurate seizure duration is important for treating physicians. It is the physician's duty to know relevant state laws about driving restrictions for patients with seizures and to inform patients of these laws or report seizures as required. Instruct patients that they should only swim with a companion and should take showers rather than baths to reduce the chance of accidental drowning.

Treatment of Epilepsy and Refractory Epilepsy

Epilepsy is a disorder of the brain characterized by the occurrence of at least one epileptic seizure and an enduring predisposition to generate epileptic seizures [1]. For some patients, the diagnosis of epilepsy can be made after a single seizure and an EEG showing characteristic epileptiform discharges. For others, the diagnosis is established only after a second seizure occurs. Almost all adults with epilepsy are treated with AEDs, and the first AED prescribed leads to seizure freedom approximately 70% of the time [32]. Up to 30% of patients, therefore, will have seizures that do not respond to the first medication. The challenge in managing this group of patients is to determine the reason for poor seizure control. It is good practice to start from scratch by retaking the patient's history, defining ictal semiology (usually with the help of an observer), asking about precipitating factors, reviewing EEG and neuroimaging findings, and inquiring about responses to past medication trials. Usually, refractory seizures may be explained by one of the following:

1. F*ocal seizures are misdiagnosed and treated as absence seizures or* vice versa. This is most often a problem in children and adolescents. Carbamazepine and phenytoin are quite effective for focal seizures but may worsen absence seizures. Ethosuximide, used exclusively for patients with absence seizures, worsens focal seizures. For patients with refractory staring spells, the duration of postictal confusion is the most reliable clinical way to distinguish between focal seizures and absence seizures: postictal confusion lasts for minutes in focal seizures and for seconds (or not at all) in absence seizures. EEG should help to differentiate between focal and absence seizures. Patients with absence seizures have characteristic generalized 3 Hz spike-wave discharges (Fig. 20.4), often

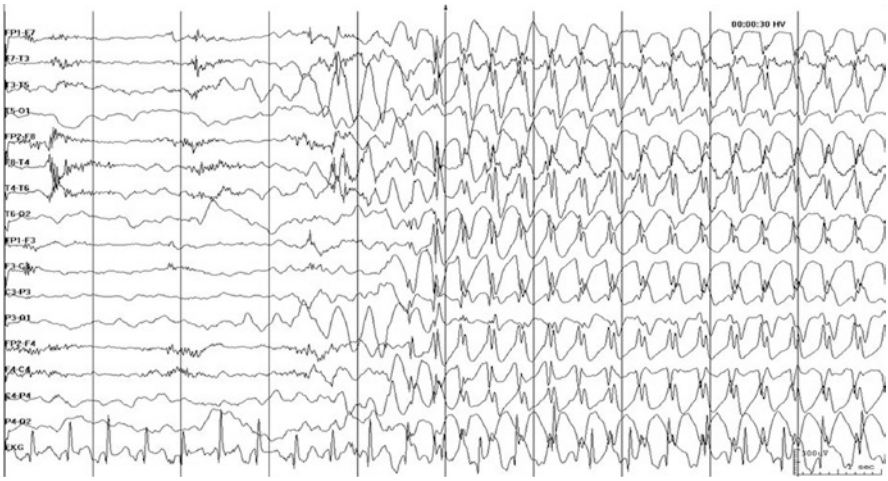

Fig. 20.4 3 Hz generalized spike-wave complexes in patient with absence seizures. (Image courtesy of Dr. Julie Roth)

elicited by hyperventilation, whereas those with focal seizures are more likely to have focal spikes or sharp waves.

2. *Lifestyle factors are lowering the seizure threshold*. Factors that lower the seizure threshold include excessive alcohol intake (and the resulting withdrawal), sleep deprivation, and stress. Lifestyle modifications, easier in principle than in practice, may reduce seizure frequency.
3. *The patient is not taking their medication.* Factors that lead to medication noncompliance include frequent dosing, high expense, and undesirable side effects. Some patients who take multiple pills per day often skip one or more of them. Others are simply not "pill people." Checking serum drug levels and counting remaining pills in prescription bottles may help to establish medication noncompliance (Table 20.3). Smartphone reminders, weekly pill boxes, and supervision by family members or visiting nurses may improve medication compliance. If appropriate, switching to medications with once-daily dosing may be helpful.
4. *The patient may not have epileptic seizures*. The differential diagnosis of seizures, including syncope, movement disorders, and psychosis, is discussed above. A conservatively estimated 20% of patients who are referred to epilepsy centers for refractory epilepsy actually have psychogenic pseudoseizures [33]. These are most often the manifestations of conversion disorders, but in some cases may be secondary to malingering. Pseudoseizures may allow patients to miss work and family responsibilities, to avoid legal actions, and to gain attention and affection. Features that suggest pseudoseizures include gradual onset and offset, asynchronous movements, preserved awareness in the presence of bilateral motor activity, forced eye closure, and development of multiple different seizure types in a short time frame. Patients with pseudoseizures have events

almost exclusively when there is an audience available to witness them, and bystanders can increase or decrease the intensity of a seizure by interacting with the patient. Pseudoseizures account for a disproportionate amount of seizures that occur in waiting rooms of doctor's offices. Elements of borderline, histrionic, and dependent personality disorders are present in many patients with pseudoseizures. These traits, however, cannot be used to make the diagnosis. Failure of serum prolactin elevation within 10–20 minutes of an event is suggestive but not diagnostic of a non-epileptic seizure [34]. Video-EEG monitoring increases the reliability of pseudoseizure diagnosis. Be aware that mesiofrontal and orbitofrontal seizures may appear bizarre and quite similar to pseudoseizures and may be missed by video-EEG monitoring [35]. These events, however, are typically quite stereotyped, unlike the events in patients with pseudoseizures. The presence of pseudoseizures does not exclude coexisting epilepsy, as approximately 10% of patients with a diagnosis of pseudoseizures will also have epileptic seizures [36]. Treating psychogenic pseudoseizures is frequently more challenging than treating epileptic seizures because patients have objectives to not get better and often resist appropriate psychiatric treatment. Patience and a frank but sensitive discussion about the nature of the events are more helpful than evasiveness and a string of ineffective and even toxic placebos.

5. *The patient may have seizures that are not adequately prevented by their current medical regimen.* If a patient continues to have seizures and appears to be tolerating their medication, try to increase their dose to the higher end of the therapeutic range. Measuring drug levels may be helpful to determine if the AED dose is adequate. If the patient does not tolerate the first medication or seizures persist despite a higher dose, try another first-line AED (see Table 20.2). Adding a second first-line agent to the first one (polytherapy) is an alternate approach that has both merits and drawbacks (see Table 20.5 and Box 20.1). An appropriate AED trial lasts five to ten times the average interval between seizures prior to its initiation (e.g., a patient with weekly seizures should have a medication trial of 5–10 weeks before judging whether it was effective) [37]. Patients with refractory seizures may require surgical evaluation (see below).
6. *The patient has a refractory epilepsy syndrome that will respond poorly to any medical or surgical treatment.* The classic example of this is Lennox-Gastaut syndrome (LGS), characterized by the triad of atypical absence, tonic, and atonic seizures. Patients with LGS are usually mentally retarded and may also have myoclonic seizures, GTCS, and focal seizures. The interictal EEG signature of LGS is the 2–2.5 Hz spike-and-wave complex (Fig. 20.5). Unfortunately, these seizures tend to be refractory to standard treatments, and creative combinations of medical and surgical therapy are usually required to reduce seizure frequency. Most patients need high doses of traditional and experimental AEDs supplemented by high doses of benzodiazepines. Medications used specifically for LGS, but rarely for other indications, include felbamate and topiramate. A variety of

Table 20.5 Suggested AED polytherapy combinations

First medication	Seizure type	Phenytoin	Carbamazepine	Valproic acid	Lamotrigine	Topiramate	Oxcarbazepine	Levetiracetam	Zonisamide	Lacosamide
Phenytoin	Partial + secondary generalized			X	X			X		X
Carbamazepine	Partial + secondary generalized			X	X			X		X
Valproate	Primary generalized including myoclonic and absence				X	X			X	
	Partial + secondary generalized	X	X		X		X	X		X
Lamotrigine	Primary generalized including myoclonic			X		X			X	
	Partial + secondary generalized			X			X	X		X
Oxcarbazepine	Partial + secondary generalized	X		X	X			X		X
Levetiracetam	Partial + secondary generalized	X	X	X	X		X			X

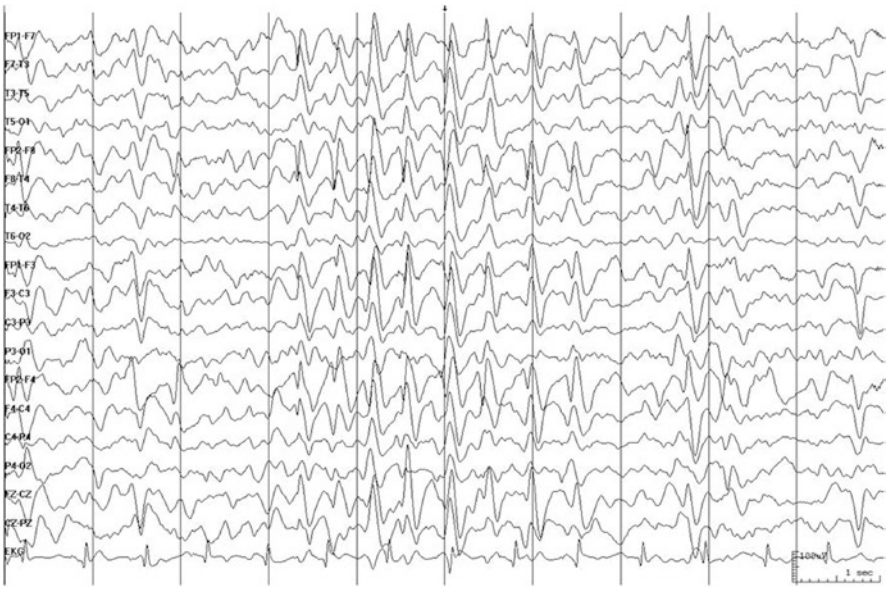

Fig. 20.5 2 Hz generalized discharges characteristic of Lennox-Gastaut syndrome. (Image courtesy of Dr. Julie Roth)

surgical therapies including corpus callosotomy and vagus nerve stimulation may be helpful. Some patients benefit from the ketogenic diet.

Box 20.1 Antiepileptic Drug Interactions

Interactions between antiepileptic drugs may become problematic in patients receiving polytherapy. The following is a brief summary of common and important drug interactions:

The older AEDs phenobarbital, phenytoin, and carbamazepine all induce hepatic P450 enzymes which in turn decrease the levels of carbamazepine, valproate, lamotrigine, topiramate, zonisamide, lacosamide, and rufinamide. It is therefore important to monitor clinical effects and medication levels closely in patients who are receiving polytherapy with these agents. Interactions may be especially complex when two of the older medications are combined.

Carbamazepine induces its own metabolism, a process which usually stabilizes 20–30 days after initiating or changing the dose [53].

Phenobarbital, phenytoin, and carbamazepine induce the uridine glucuronyl transferases which metabolize lamotrigine. Patients taking lamotrigine, therefore, may require higher doses.

Valproate inhibits the metabolism of phenobarbital, phenytoin, carbamazepine, lamotrigine, and rufinamide. The reduced metabolism of lamotrigine is particularly important, as it may lead to toxicity. For patients already taking valproate, lamotrigine should be started at half the typical dose and titrated half as quickly. Valproate displaces phenytoin from its protein-binding sites, leading to an increase in the free serum concentration of phenytoin.

Epilepsy Surgery

Because seizure control with a third AED after two unsuccessful medication trials is unlikely, consider epilepsy surgery evaluation for patients with poorly controlled seizures despite adequate trials of two AEDs [38]. Presurgical evaluation is usually done by a multidisciplinary group including a neurologist, neurosurgeon, clinical psychologist, and epilepsy nurse. The evaluation of potential candidates begins with an MRI of the brain to look for surgically correctable structural abnormalities and inpatient video-EEG monitoring to localize the seizure focus. Ictal SPECT studies involve injecting a radioactive tracer intravenously at the earliest stage of a seizure and monitoring for increased blood flow in a seizure focus during a seizure. If a seizure focus is well localized, testing proceeds with evaluation of language and memory (including an intracarotid sodium amobarbital or Wada test, transcranial magnetic stimulation, and neuropsychological evaluation) to minimize the chance that resection will produce adverse cognitive or behavior effects. Diagnostic epilepsy surgery, specifically implantation of grid and strip EEG electrodes, improves the chances of precise localization of seizure foci and targeted resection. Surgical options include curative resection of a seizure focus (e.g., temporal lobectomy) and palliative surgeries such as corpus callosotomy and multiple subpial transections, which are used in patients with severe refractory seizure disorders including LGS. Among patients who undergo resection of a seizure focus, those who have temporal lobectomy have a better long-term outcome than those who undergo occipital and parietal resections, and patients who undergo frontal lobe resection are the least likely to achieve seizure freedom [39]. While corpus callosotomy and multiple subpial transections for severe epilepsy syndromes do not usually result in seizure freedom, they may decrease seizure frequency enough to have a positive impact on a patient's quality of life.

Vagus Nerve Stimulation

The vagus nerve stimulator (VNS) is a pacemaker-like device which is implanted under the left clavicle with electrical leads that then wrap around the left vagus nerve. Stimulation of the vagus nerve reduces seizure frequency and aborts seizures, possibly by activating neuronal networks in the thalamus and limbic system [40]. Meta-analysis of VNS efficacy data shows that approximately 45% of patients who undergo implantation achieve a 50% reduction in seizure frequency [40]. Seizure freedom, however, is rare following VNS. Common side effects of VNS include hoarseness, throat pain, and cough, all of which may be remedied by adjusting device parameters.

Status Epilepticus

Status epilepticus is defined as continuous seizure activity or two or more seizures with incomplete recovery of consciousness in between seizures lasting for at least 5 minutes [41]. Status epilepticus is divided into convulsive and nonconvulsive

types. Convulsive status epilepticus (repetitive generalized tonic-clonic seizures) is a true medical emergency which will be the focus of this section. Nonconvulsive status epilepticus is discussed further in Chap. 2. Because it is easy to panic when dealing with a patient in convulsive status epilepticus, it helps to have a systematic approach to reduce uncertainty and understand the management options.

Step 1: Life Support

Protecting the airway (with intubation if necessary) and obtaining intravenous access are the first steps in managing status epilepticus. Although some AEDs may be given intramuscularly or rectally, most AEDs used for status epilepticus require intravenous access. When establishing access, draw blood for laboratory studies including complete blood count, chemistry panel, liver function tests, AED levels, and toxicology screens. If the patient is not awake, it is important to initiate bedside EEG monitoring to determine the patient's response to any of these interventions.

Step 2: Abort Seizures

Phase 1: Benzodiazepines

Intravenous lorazepam (0.1 mg/kg) or diazepam (0.15 mg/kg) will abort status epilepticus in approximately 2/3 of patients [42, 43]. A typical approach is to give 4 mg IV lorazepam once and then to repeat the 4 mg dose in 5–10 minutes if the status epilepticus has not resolved. If the patient lacks intravenous access at seizure onset, alternative benzodiazepine choices include diazepam (20 mg rectally) or midazolam (10–20 mg intramuscularly) [44].

Phase 2: Intravenous AEDs

Treat patients who do not respond to lorazepam with intravenous fosphenytoin (20 mg/kg), valproate (25–40 mg/kg over 15 minutes), or levetiracetam (1000–3000 mg) [45]. Fosphenytoin is preferred to phenytoin because it can be administered safely through peripheral intravenous lines and can be infused three times faster than phenytoin.

Phase 3: AEDs That Require Intubation

Patients with status epilepticus that is refractory to lorazepam and fosphenytoin almost always require transfer to an intensive care unit and stronger medications that necessitate intubation. Patients with refractory status epilepticus should also be monitored with continuous video-EEG. The treatment options are:

- Phenobarbital 15 mg/kg IV
- Midazolam 0.2 mg/kg loading dose followed by 0.75–10 μg/kg/min continuous infusion
- Propofol 1–2 mg/kg loading dose followed by 2–10 mg/kg/hr continuous infusion

The most important side effects of these agents are hypotension and sedation. The propofol infusion syndrome is characterized by metabolic acidosis, rhabdomyolysis, and multiple organ failure and is best prevented by using a dose below 5 mg/kg/hr.

Phase 4: Pentobarbital Coma

If phenobarbital, midazolam, or propofol fails to control status epilepticus, the next line of treatment is pentobarbital coma. Patients must be attached to continuous bedside EEG telemetry, as they will not have any motor manifestations of status epilepticus to monitor treatment outcome. Pentobarbital is loaded at a dose of 5 mg/kg followed by IV infusion of 1–10 mg/kg/hr, titrated gradually upwards to a burst-suppression pattern on EEG (Fig. 20.6). Pentobarbital coma is typically maintained for 24 hours, at which point the medication is weaned gradually, using EEG for guidance.

Phase 5: Superrefractory Status Epilepticus

The term "superrefractory status epilepticus" refers to status epilepticus that continues after more than 24 hours of anesthetic therapy or after attempted anesthetic withdrawal [46]. Unfortunately, there are no large studies on this form of status epilepticus, and evidence for treatment efficacy is nearly entirely anecdotal. Options that have been employed successfully include steroids, ketamine, the ketogenic diet, hypothermia, transcranial magnetic stimulation, deep brain stimulation, electroconvulsive therapy, and surgical resection of a presumed seizure focus.

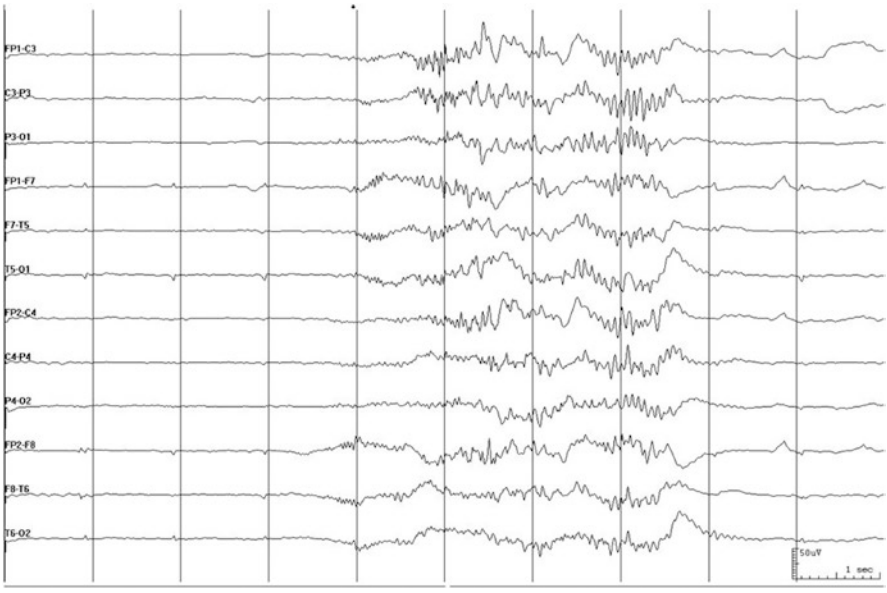

Fig. 20.6 Burst suppression in a patient with status epilepticus being treated with pentobarbital coma. (Image courtesy of Dr. Julie Roth)

Step 3: Determine the Underlying Etiology of Status Epilepticus

Once seizure control is established, focus on determining the etiology of status epilepticus. Obtain collateral history if possible, with special attention to a prior history of epilepsy and AED use. Common precipitants of status epilepticus include medication noncompliance, alcohol withdrawal, infections (especially meningitis and encephalitis), metabolic disturbances, acute strokes, tumors, drug overdose, and cardiac arrest [47]. If a clear cause of status epilepticus is not identified from the initial history and laboratory studies, expand the evaluation to include neuroimaging and cerebrospinal fluid analysis. The etiologies of refractory status epilepticus are quite similar to those which cause encephalopathy, as described in Chap. 1. The term new-onset refractory status epilepticus (NORSE) is used to describe patients without a pre-existing seizure disorder who develop status epilepticus and presumably represents an inflammatory or autoimmune condition [48].

Step 4: Prevent Further Episodes

Correcting the proximate cause of status epilepticus is the first step in preventing recurrence. Some patients with provoked seizures may not require new medications. Patients with known epilepsy need AED regimen modification to prevent seizure recurrence. Medication noncompliance and other seizure precipitants must be addressed, if relevant.

Sudden Unexpected Death in Epilepsy (SUDEP)

SUDEP refers to the sudden, unexpected death of a patient with epilepsy that is not related to trauma, drowning, a witnessed seizure, or other identified autopsy-confirmed causes of death. In adults, the rate of SUDEP is estimated at 1.2 cases per 1000 person-years [49]. The main risk factor for SUDEP is uncontrolled generalized tonic-clonic seizures [50]. It is difficult to broach the topic of SUDEP with patients at any point during the course of seizures or epilepsy, especially at a first encounter, and patients seldom ask about it. Introducing the concept early may encourage AED compliance but may also provoke unnecessary anxiety and stress. Nocturnal supervision including a bed partner, listening device, or automated seizure monitor may help to reduce the risk of SUDEP [51].

Withdrawing AEDs

Slow AED tapering over 2–3 months may be appropriate for patients with long periods of seizure freedom. In patients who are seizure-free for at least 2 years, the probability of seizure freedom over the next 2 years is approximately 80% in patients who continue to take AEDs and 60% in those who discontinue them [42].

Ideal candidates for medication withdrawal have normal neurologic examinations, normal neuroimaging studies, and normal EEG results. Favorable prognostic factors include longer periods of seizure freedom, use of a single AED to achieve seizure freedom, and a lack of tonic-clonic seizures. It is important to involve the patient in the discussion about medication withdrawal: some are eager to discontinue their AEDs, while others enjoy a greater peace of mind if they continue to take their medications.

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Stroke

21

Stroke and Transient Ischemic Attack

Stroke is a sudden-onset neurologic syndrome caused by infarction or hemorrhage within the central nervous system. The term transient ischemic attack (TIA) refers to "a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction" [1]. The gravity of a TIA must not be minimized, as it shares an identical group of pathophysiologies with "completed" strokes and is associated with similar risk for recurrence.

Common Stroke Syndromes

While there is no substitute for a detailed understanding of vascular neuroanatomy, recognizing a small group of common stroke syndromes is a powerful bedside tool for localization and diagnosis.

Anterior Circulation Ischemic Strokes

Middle Cerebral Artery (MCA) Syndromes

The anatomy of the circle of Willis, including the origin of the MCA, is shown in Fig. 21.1. The MCA is one of the two main branches of the internal carotid artery, and infarction of the MCA or its branches is one of the most common causes of stroke. The first important branches of the MCA are the lenticulostriate arteries which arise from the stem of the artery and supply the caudate nucleus, internal capsule, putamen, and lateral globus pallidus. After giving rise to the lenticulostriate arteries, the MCA most commonly divides into superior and inferior divisions. The superior division supplies the frontal lobe, while the inferior division supplies the superior temporal lobe [2]. The parietal lobe may be supplied by either the superior

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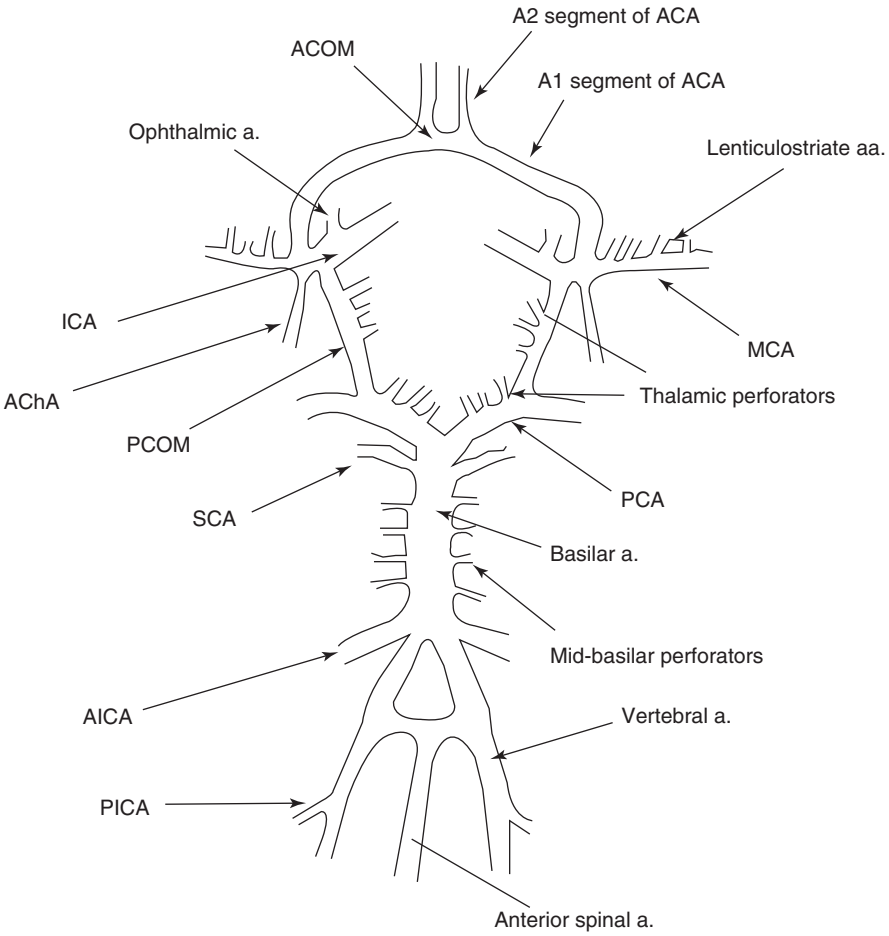

Fig. 21.1 The circle of Willis. ACA anterior cerebral artery, AChA anterior choroidal artery, ACOM anterior communicating artery, AICA anterior inferior cerebellar artery, ICA internal carotid artery, MCA middle cerebral artery, PCA posterior cerebral artery, PCOM posterior communicating artery, PICA posterior inferior cerebellar artery, SCA superior cerebellar artery

or inferior division of the MCA or by both. Depending on the site of occlusion, MCA strokes lead to the following sensorimotor abnormalities:

- Occlusion at the stem of the MCA produces a severe contralateral hemiplegia, contralateral hemisensory loss, and ipsilateral eye deviation. Stem occlusion may lead to the "malignant MCA syndrome" in which swelling of the infarcted territory produces increased intracranial pressure and potentially cerebral herniation and death (see below and Chap. 2).

- Infarction of the MCA distal to the takeoff of the medial lenticulostriate arteries produces contralateral weakness of the face and arm and may be associated with ipsilateral eye deviation. Hemiparesis tends to be milder than when the occlusion takes place at the stem of the artery.
- Superior division infarction typically produces contralateral weakness and numbness which are greatest in the face and hand.
- Inferior division infarction results in mild contralateral face and hand weakness and numbness and sometimes a contralateral homonymous hemianopia.

In addition to sensorimotor abnormalities, MCA infarction often produces behavioral manifestations referable to the affected hemisphere:

- Left MCA: The characteristic behavioral manifestation of left MCA infarction is aphasia, the acquired loss of language (see Chap. 3). Complete left MCA infarction in a patient with left hemispheric dominance for language would be expected to produce global aphasia. Broca aphasia is associated with superior division infarction, whereas Wernicke aphasia is associated with inferior division infarction.
- Right MCA: The classical behavioral manifestation of a right MCA stroke is left-sided hemineglect (see Chap. 1). Stroke involving the inferior division of the right MCA may produce an acute agitated delirium [3].

Anterior Cerebral Artery (ACA) Syndrome

The ACA is derived from the internal carotid artery (Fig. 21.1). The proximal ACA, or A1 segment, connects the internal carotid artery and the anterior communicating artery (ACOM). The distal ACA (beginning with the A2 segment) arises from the ACOM and contains most of the branches which supply the medial frontal and parietal lobes. ACA infarction is uncommon. It classically results in contralateral leg weakness that is greatest in the foot, although only a minority of strokes that produce isolated or predominant leg weakness are secondary to ACA infarcts [4]. Sensory deficits in the leg and foot are usually modest. Stroke involving the left anterior cerebral artery may produce transcortical motor aphasia (Chap. 3). An important anatomic variant is an azygous ACA in which both distal segments arise from the same A1: occlusion at the single origin leads to infarction of both distal ACA territories and, therefore, bilateral leg weakness.

Internal Carotid Artery (ICA)

The common carotid artery bifurcates into the ICA and external carotid artery in the neck at approximately the level of the fourth cervical vertebra. The ICA enters the skull via the carotid canal and crosses the foramen lacerum before entering the cavernous sinus. After emerging from the cavernous sinus, the carotid artery gives rise to the ophthalmic artery and then trifurcates into the ACA, MCA, and posterior communicating (PCOM) arteries (Fig. 21.1). The anterior choroidal artery (AChA)

usually arises from the ICA just distal to the trifurcation. The following are the common ICA stroke syndromes.

- ICA occlusion. Occlusion of the ICA results in the combination of the MCA and ACA syndromes. Deficits are usually severe and may be life-threatening if a large volume of brain is infarcted and massive edema occurs. Deficits may be milder if the occlusion develops slowly, after collateralization from the contralateral carotid system or posterior circulation has been established.
- Distal embolization. Distal emboli from the ICA most commonly lodge in the MCA, the ophthalmic artery, or the retinal artery branches. Stroke involving the retinal artery or its branches causes monocular blindness, which, if transient, leads to the clinical syndrome of amaurosis fugax (Chap. 5).
- Watershed infarction. The ischemic watershed or borderzone refers to an area of the brain perfused by the end distributions of two vascular territories. Because the watershed areas have the most tenuous blood supplies, they are prone to infarction during episodes of systemic hypotension (often in the context of cardiac arrest). The most common watershed syndrome involves the territory which is jointly perfused by the ACA and MCA, leading to weakness with or without sensory disturbance of the proximal arm and leg, the so-called "man-in-the-barrel" syndrome.
- Carotid artery dissection. Headache, ipsilateral eye pain, and Horner syndrome are the most common symptoms of carotid artery dissection (Chap. 19). These symptoms may be accompanied or followed by symptoms of distal embolization.
- Anterior choroidal artery (AChA) infarction. The AChA is usually a branch of the ICA, but it may also arise from the MCA or the PCOM. The AChA variably supplies blood to the motor and sensory fibers within the posterior limb of the internal capsule, the optic tract, the lateral geniculate body, and the optic radiations. The AChA syndrome, uncommon and usually incomplete, includes components of contralateral weakness, sensory loss, and homonymous hemianopia.

Posterior Circulation Ischemic Strokes

The vertebral arteries are derived from the subclavian arteries in the chest and ascend through the foramen transversarium of the C2-6 vertebrae. They then pass through the foramen magnum to enter the skull. The vertebral arteries give rise to the posterior inferior cerebellar arteries at the inferior medullary level and send branches to the anterior spinal artery at the mid-medullary level (Fig. 21.1). The vertebral arteries then fuse at the pontomedullary junction to form the basilar artery. The anterior inferior cerebellar arteries are the first branches of the basilar artery. Penetrating branches arise from the basilar artery as it runs along the ventral surface of the pons. The superior cerebellar arteries and the posterior cerebral arteries are the next branches. Finally, the basilar artery gives rise to the paired posterior

communicating arteries which anastomose with the anterior circulation. Posterior circulation infarction is often patchy, producing a variety of deficits such as diplopia, dysarthria, facial and body numbness, vertigo, and nausea and vomiting. Nonetheless, there are several well-defined posterior circulation syndromes:

Wallenberg Syndrome

Occlusion of the vertebral or (less commonly) the posterior inferior cerebellar artery results in infarction of the lateral medulla, leading to the Wallenberg syndrome (Fig. 21.2). Common symptoms of Wallenberg syndrome include vertigo, nausea, vomiting, facial pain, dysarthria, dysphagia, and ipsilateral limb ataxia. Examination findings include ocular misalignment due to skew deviation, nystagmus, loss of pinprick sensation in the ipsilateral face and contralateral body, ipsilateral Horner syndrome, and ipsilateral limb ataxia.

Mid-basilar Artery Occlusion

The basilar artery runs along the midline of the ventral pons. Complete occlusion of the basilar artery deprives the descending bilateral corticospinal and corticobulbar

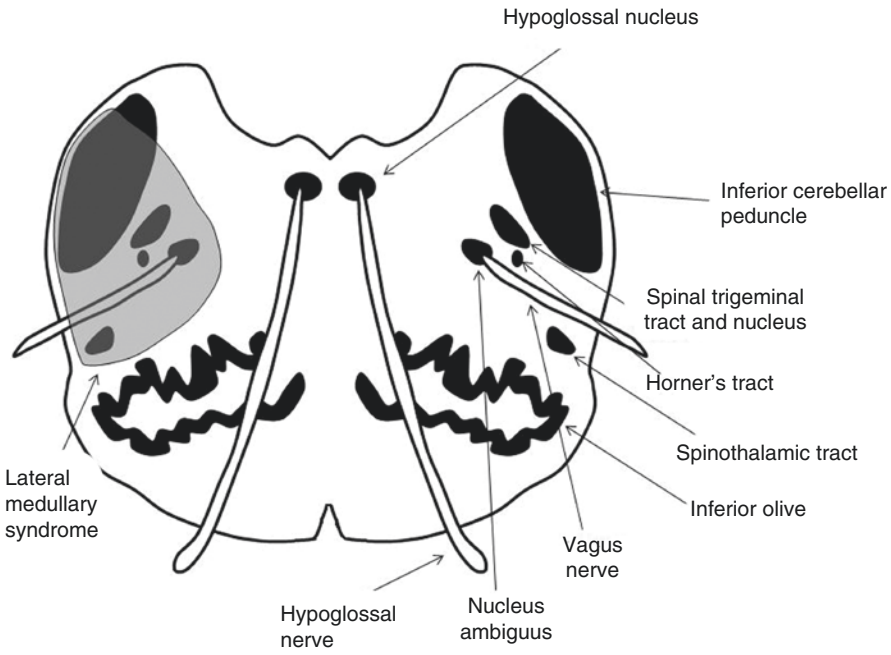

Fig. 21.2 Cross section of the medulla showing the structures involved in a laterally medullary infarction (Wallenberg syndrome). Although there is considerable variety among patients with this syndrome, typical features include vertigo and ipsilateral limb ataxia (inferior cerebellar peduncle), ipsilateral facial sensory loss (spinal trigeminal tract and nucleus), contralateral hemibody sensory loss (spinothalamic tract), ipsilateral Horner syndrome (Horner tract), and dysphagia (nucleus ambiguus and vagus nerve)

tracts of their blood supplies, leading to the locked-in syndrome (Chap. 2) in which the patient is completely paralyzed with the exception of preserved vertical eye movements and blinking. Consciousness is preserved because the midbrain and thalamus, which contain key components of the ascending arousal system, are spared.

Mid-basilar Penetrating Branch Occlusion

Occlusion of one of the smaller penetrating branches of the mid-basilar artery most commonly produces contralateral hemiparesis due to infarction of the corticospinal tract in the pons. If the abducens or facial nerve fascicles are involved in the pontine tegmentum, ipsilateral eye abduction (Chap. 6) and ipsilateral facial palsy may accompany the hemiparesis (Chap. 8).

Rostral Basilar ("Top of the Basilar") Occlusion

Occlusion of the rostral basilar artery produces a variety of ocular motor and behavioral manifestations, most commonly vertical gaze and convergence impairments [5]. In many cases, the distal basilar branches (the SCA and PCA) are also involved. Therefore, there is no single unifying clinical feature of rostral basilar occlusion.

Posterior Cerebral Artery (PCA) Infarction

The PCA supplies the visual cortex in the occipital lobes. Visual abnormalities are therefore the most consistent manifestations of PCA infarction (Chap. 5):

- Unilateral PCA infarction leads to macular-sparing contralateral homonymous hemianopia. Because horizontal eye movements allow some compensation for this visual loss, the patient may fail to recognize this problem until their visual fields are tested at bedside.
- Bilateral PCA infarctions result in complete visual loss. In some cases, a patient with bilateral PCA infarction may deny that they are blind and confabulate a detailed visual scene (Anton syndrome).
- Infarction of the left PCA may produce alexia without agraphia.
- Occasionally, PCA infarction may lead to a state of agitated confusion (Chap. 1) [6].

Thalamic Strokes

Thalamic strokes produce a heterogeneous group of clinical deficits. The arterial supply of the thalamus is derived from the posterior cerebral and posterior communicating arteries and is quite variable. The common vascular syndromes of the thalamus involve the following four arteries [7]:

- Thalamogeniculate artery. This artery supplies the lateral thalamus, and infarction leads to contralateral hemibody numbness (see *pure sensory lacunar* below).

- Paramedian thalamic-subthalamic artery. Medial thalamic infarction leads to problems with consciousness, behavior, and vertical gaze. These patients often present in coma and, when they awaken, appear confused or apathetic (Chap. 2).
- Polar artery. Infarction of the anterior pole of the thalamus leads to a variety of behavioral manifestations including amnesia, aphasia, and confusion, in some cases causing "sudden-onset dementia" (Chap. 4).
- Posterior choroidal artery. This artery supplies the lateral geniculate body and leads to contralateral homonymous field deficits, most characteristically the loss of a central wedge of vision (Chap. 5). Additional deficits may include hemiparesis, hemisensory loss, and neuropsychological disturbances including aphasia.

Cerebellar Strokes

The three arteries that supply blood to the cerebellum are the superior cerebellar artery (SCA), the anterior inferior cerebellar artery (AICA), and the posterior inferior cerebellar artery (PICA). Typical features of cerebellar strokes include occipital-nuchal headache, nausea and vomiting, ataxia, and dysarthria. In some cases, isolated cerebellar infarctions may produce only vertigo and thus resemble a more benign condition such as labyrinthitis (Chap. 9). Unless the adjacent brainstem is involved, it may be difficult to distinguish among infarctions in the three arterial territories (Table 21.1). Although the majority of cerebellar infarcts produce mild, temporary deficits, larger strokes may lead to hydrocephalus or life-threatening brainstem compression if untreated.

Lacunar Strokes

Lacunar strokes are small vessel occlusions that usually occur in the context of hypertension and atherosclerotic disease [8]. The following are the most common lacunar syndromes:

- Pure motor lacunar. Infarction in the posterior limb of the internal capsule, corona radiata, base of the pons, or cerebral peduncle may result in a contralateral hemiparesis affecting the face, arm, and leg without sensory or behavioral manifestations.

Table 21.1 Cerebellar stroke syndromes

Territory	Extracerebellar structures affected	Extracerebellar signs and symptoms
Superior cerebellar artery	Midbrain, thalamus, occipital lobes	"Top of the basilar" syndrome
Posterior inferior cerebellar artery	Dorsolateral medulla	Wallenberg syndrome
Anterior inferior cerebellar artery	Lateral pons	Ipsilateral facial weakness, ipsilateral facial/contralateral body numbness, and hearing loss

- Pure sensory lacunar. Lacunar infarction of the ventroposterior thalamus (ventroposterolateral and ventroposteromedial nuclei) leads to the sudden onset of contralateral numbness of the face, arm, and leg.
- Ataxic hemiparesis. Small vessel infarction involving the base of the pons or subcortical white matter may produce contralateral limb weakness and ataxia. The foot tends to be weaker than the hand, which in turn tends to be weaker than the face.
- Dysarthria-clumsy hand. Lacunes involving the base of the pons or the genu of the internal capsule may produce severe dysarthria with contralateral face and hand weakness.

Intracranial Hemorrhage (ICH)

ICH accounts for approximately 20% of strokes. It presents in a very similar or identical manner to ischemic stroke but is more likely to progress over minutes to hours. It is often difficult to distinguish between hemorrhage and infarction by history and physical examination alone. Although headache makes ICH slightly more likely than ischemic stroke, neuroimaging studies are much more reliable in distinguishing between the two stroke types. Evaluation and treatment of ICH is discussed in greater detail below.

Cerebral Venous Thrombosis

Venous strokes are much less common than arterial ones. Susceptible populations include women in the puerperium, patients with hereditary coagulation defects, and patients with systemic inflammatory diseases. Because headache is the most common presentation of venous sinus thrombosis, it is discussed in more detail in Chap. 19.

Spinal Cord Strokes

Spinal cord strokes are rare compared to cerebral strokes. Classic syndromes including the anterior spinal artery syndrome and transverse spinal cord infarction are discussed further in Chap. 17.

Stroke Mimics

The rapidity of symptom onset which characterizes stroke is not unique, and in approximately 1/3 of cases, sudden-onset neurologic deficits are produced by other medical, neurological, or psychiatric conditions [9].

Acute Confusional State

While acute confusional states may occasionally be secondary to stroke in the distribution of the left posterior cerebral or right middle cerebral arteries, they are more commonly secondary to toxic or metabolic disturbances [6, 10]. Evaluation of confusion is discussed further in Chap. 1.

Focal Neuropathies

Deep sleep, usually secondary to heavy intoxication or surgery, may lead to a sudden-onset, painless focal neuropathy that mimics stroke. The best-known focal neuropathy of this type is the "Saturday night palsy," a radial nerve palsy that occurs when a patient awakens with a wrist drop after a night of sleeping with their arm draped over a chair or bed. Other nerves that are susceptible to focal injuries mimicking stroke include the ulnar, sciatic, and common peroneal nerves. The techniques to distinguish between stroke and focal neuropathy are discussed in further detail in Chap. 11. While physical examination may help to differentiate focal neuropathies from stroke in most cases, neuroimaging studies or electromyography are often required to solidify the diagnosis. It is important to exercise caution in diagnosing a focal neuropathy rather than a stroke, as infarction of the "hand knob" area of the cerebral cortex may resemble a radial or ulnar neuropathy quite closely [11].

Metabolic Insult Causing Re-expression of Old Stroke (MICROS)

MICROS is the apparent return of prior stroke deficits when patients are subjected to metabolic insults, most commonly urinary tract infections, pneumonia, or medication toxicity. The pathophysiology of MICROS is not well understood, but it is likely that tissue that has undergone neural repair during stroke recovery is susceptible to relatively small metabolic perturbations which do not affect otherwise healthy brain tissue. MICROS should be considered only after thorough evaluation excludes the presence of an actual stroke. Treat MICROS by correcting the responsible medical condition: deficits usually improve, sometimes in a few hours, but more often over the course of several days.

Migraine Aura

Migraine aura may resemble stroke when it is not followed by headache (Chap. 19). Usually, though, the tempo and progression of deficits help to distinguish between migraine aura and stroke. Focal deficits in migraine aura are typically followed by symptoms which develop over several minutes when adjacent cortical areas become involved by a wave of spreading depression. Stroke deficits, on the other hand, are maximal at onset and progress very little if at all. Younger patients with a history of

migraine do not require further evaluation for stroke. Older patients and those without any prior history of aura, however, require detailed investigation for stroke including neuroimaging studies before the diagnosis may be made comfortably.

Todd Paralysis

A combination of neuronal exhaustion and inhibition following a seizure may produce a variety of clinical deficits including focal numbness, visual field cuts, and aphasia (Chap. 20). The most well-known postictal deficit is Todd paralysis, characterized by focal weakness following a motor seizure. Todd paralysis and related postictal phenomena are most likely to be misdiagnosed as stroke when the preceding seizure is not witnessed.

Transient Global Amnesia (TGA)

TGA is an acute-onset amnestic state in which a patient loses the ability to encode new memories (Chap. 1) [12]. The patient with TGA characteristically repeats the same questions every 2–5 minutes but is otherwise capable of performing cognitive tasks at their typical level. An episode typically lasts for several hours and resolves spontaneously. The exact pathophysiology of TGA is unclear, with cerebral infarction being confirmed only rarely.

Subdural Hematoma (SDH)

The protean manifestations of SDH include hemiparesis, seizures, and confusion, and even an experienced neurologist may miss the diagnosis by failing to consider it. In the presence of a typical history of head trauma with headache and focal neurological signs, the diagnosis of SDH is straightforward. Head trauma, however, is often forgotten, leading to a diagnostic delay of several days or weeks. Non-contrast head CT is the diagnostic study of choice (Fig. 21.3). The first step in treating SDH is to prevent further hematoma expansion by reversing anticoagulation (see below). Indications for neurosurgical intervention include significant midline shift, progression of neurologic deficits, or expansion of hematoma size on serial CT scans. Many patients, especially those with small subdural hematomas, recover without intervention when the blood is reabsorbed.

Convexal Subarachnoid Hemorrhage

Atraumatic, non-aneurysmal subarachnoid hemorrhage overlying the cerebral convexities is another condition that may resemble an ischemic or hemorrhage stroke [13]. Headache may be the first symptom, but patients may also present with a TIA type of syndrome. MRI shows superficial cortical hemorrhage (Fig. 21.4). In most patients, cortical subarachnoid hemorrhage is self-limited, though it may recur.

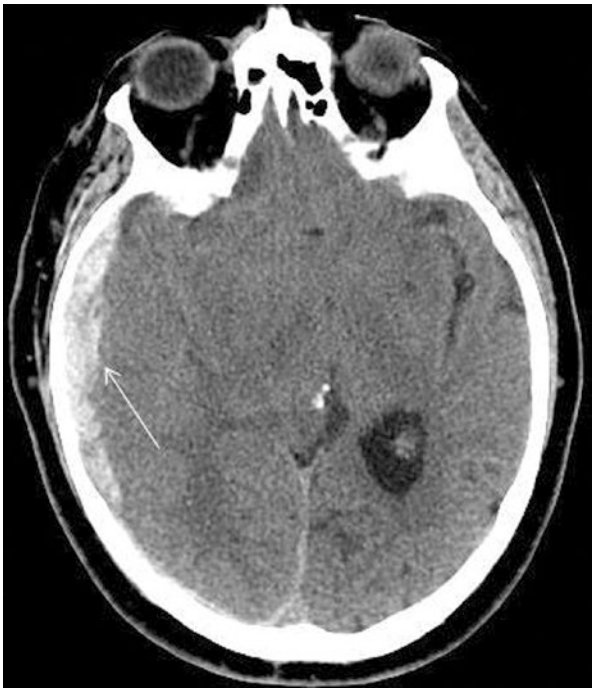

Fig. 21.3 Non-contrast head CT showing right subdural hematoma. Note the presence of midline shift

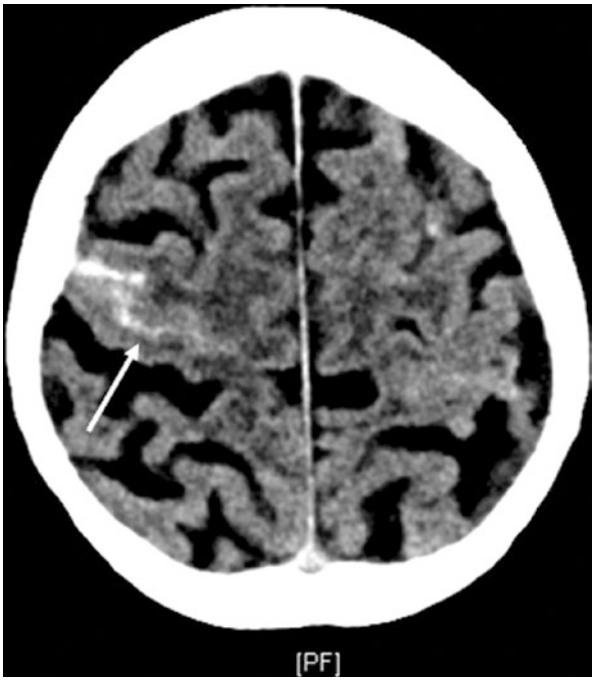

Fig. 21.4 Non-contrast head CT demonstrating convexal subarachnoid hemorrhage

Hypoglycemia and Hyperglycemia

Both high and low blood sugar levels may result in focal neurological deficits that closely resemble acute ischemic stroke. Restoring normoglycemia usually resolves any deficits in a few hours, but improvement may sometimes take several days.

Psychogenic Disorders

Psychogenic disorders, especially malingering and conversion disorders, may mimic stroke. While these conditions are often obvious, mimicry of true neurologic deficits may be precise enough to require neuroimaging to secure the diagnosis.

Peripheral Vestibulopathy

Peripheral vestibulopathy is often difficult to separate from central causes of vertigo such as brainstem or cerebellar infarction (Chap. 9).

Bell's Palsy

Bell's palsy is acute facial weakness caused by a peripheral lesion of the facial nerve and is discussed further in Chap. 8.

Physical Examination

Every patient with a suspected stroke requires comprehensive neurologic examination to define its clinical effects. Cardiovascular and funduscopic examinations are the most important components of the general physical examination. Auscultation of a heart murmur or atrial fibrillation points to a potential cardioembolic source of stroke. A carotid bruit is often a nonspecific finding of systemic atherosclerosis. A long, high-pitched bruit located high within the neck at the carotid bifurcation, however, is more suggestive of carotid artery stenosis [14]. Funduscopic examination may disclose Hollenhorst plaques which are bright white particles that appear at retinal vascular bifurcations and usually suggest an embolic stroke source from the ipsilateral carotid artery or the heart. In patients with central retinal artery occlusion, fundoscopy shows macular pallor and a cherry-red spot in the fovea (Chap. 5).

Laboratory Studies

All patients evaluated for suspected acute stroke require a routine set of laboratory tests, including a complete blood count, basic metabolic profile, coagulation studies, urinalysis, toxicology screen, and chest X-ray. While these tests may have only limited utility in defining the etiology of stroke, they help to diagnose stroke

mimics, screen for conditions that may worsen stroke outcome, and determine whether patients are eligible for intravenous thrombolysis.

Neuroimaging

Neuroimaging studies are essential in differentiating between ischemic and hemorrhagic strokes, help to establish the diagnosis when the history or physical examination are unreliable, point to alternative diagnoses such as brain tumor or subdural hematoma, and help to define stroke pathophysiology. Remember that neuroimaging studies are complementary to the history and examination and that all radiographic abnormalities must be placed in the appropriate clinical context.

Non-contrast Head CT

Non-contrast head CT is usually the first and often the only neuroimaging study performed because it is widely available and can be obtained rapidly. In many cases, patients with suspected stroke have already had a head CT before neurological consultation is requested. The main use of CT scan is to detect intracranial hemorrhage (Fig. 21.5). The CT changes suggestive of acute ischemic stroke have only modest sensitivity and interobserver reliability (Table 21.2) [15, 16].

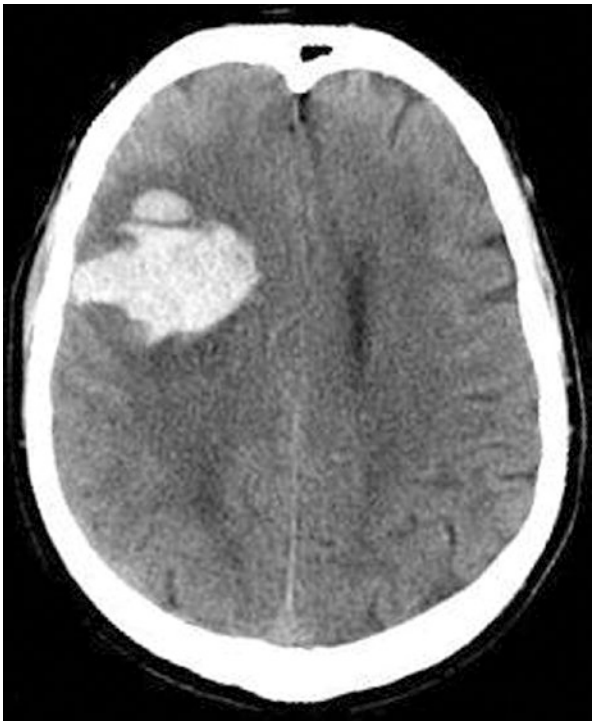

Fig. 21.5 Non-contrast head CT showing an intracranial hemorrhage

Table 21.2 CT changes in early ischemic stroke

Obscuration of the lentiform nucleus
Cortical sulcal effacement
Loss of insular ribbon
Hyperdense middle cerebral artery
CT dot sign
Loss of gray-white differentiation in basal ganglia

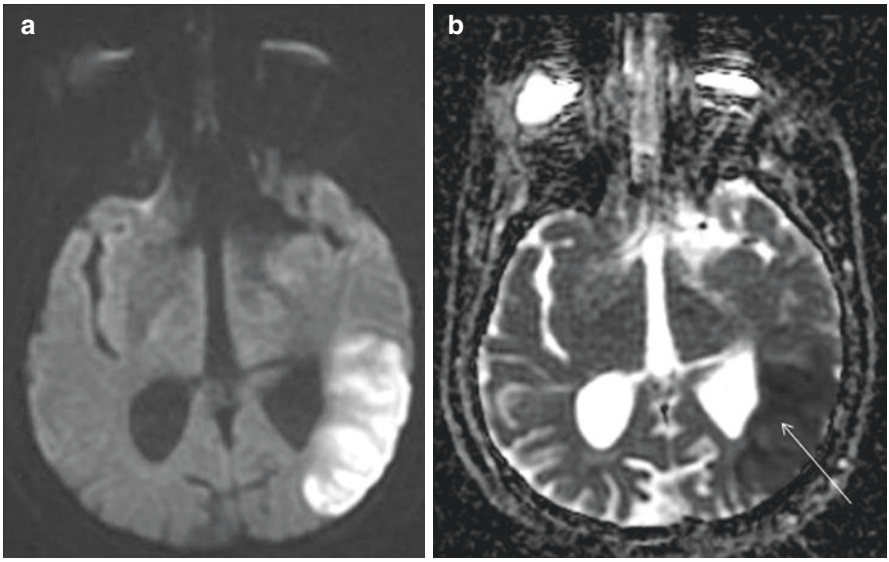

Fig. 21.6 An acute occipital-temporal infarction as captured by (**a**) diffusion-weighted imaging (DWI) and (**b**) the apparent diffusion coefficient (ADC) map

Diffusion-Weighted MRI (DWI)

DWI is the imaging study of choice for acute ischemic stroke. A bright DWI signal reflecting cytotoxic edema appears within 15–30 minutes of ischemic stroke onset, and its high sensitivity for acute stroke makes it ideal for evaluating patients with confusing or atypical presentations (Fig. 21.6a) [17]. Approximately 1/3 of patients with transient ischemic attacks will show slowed diffusion in a relevant area of the brain [18]. DWI has two minor limitations. First, it may be insensitive to very small strokes, particularly those involving the brainstem. Second, old T2 lesions may "shine through" and appear bright on DWI, falsely suggesting an acute infarction. The way to differentiate between newly infarcted tissue and an old T2 lesion is by looking at the apparent diffusion coefficient (ADC) map. Acute infarction is bright on DWI, is dark on the ADC map, and remains dark on the ADC map for less than 10 days (Fig. 21.6b) [19]. Older T2 hyperintensities are bright on both DWI and the ADC map. Slowed diffusion is highly specific for acute ischemia in appropriately selected patients, though diffusion may be abnormally slow in patients with focal seizures, encephalitis, or acute inflammatory conditions [20, 21].

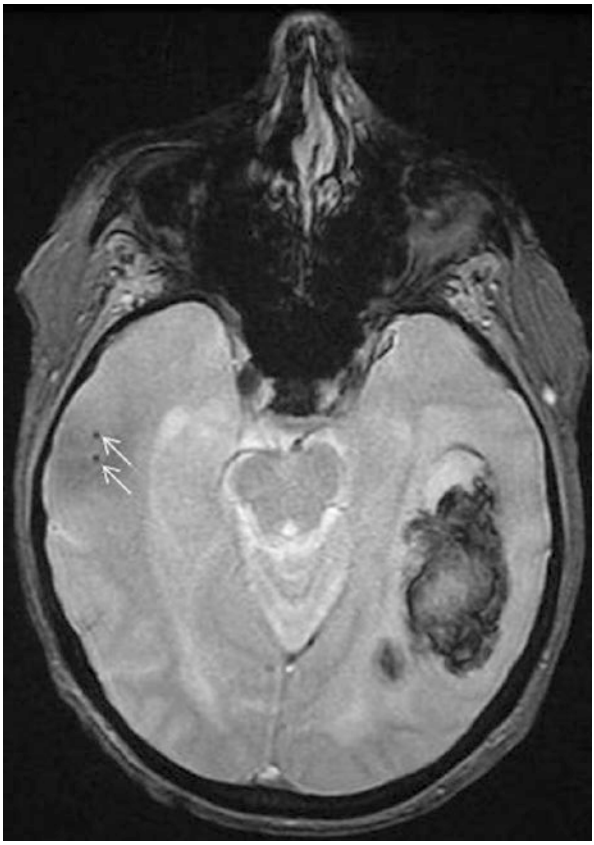

Fig. 21.7 Susceptibility imaging shows left temporal-parietal hemorrhage. Note the presence of two cerebral microbleeds in the right temporal lobe (arrows), likely reflective of amyloid angiopathy

Susceptibility Images

Gradient echo susceptibility-weighted MR imaging (also referred to as T2*) is useful for detecting hemorrhage (Fig. 21.7). Susceptibility images are as sensitive as non-contrast head CT scan in detecting acute blood [22].

Vascular Imaging Studies

Vascular imaging studies such as magnetic resonance angiography (MRA – Fig. 21.8) and computed tomographic angiography (CTA) are useful in defining the specific vessel responsible for a stroke. CTA is required for patients who may be candidates for mechanical thrombectomy. Other vascular imaging studies that may help in the acute setting include CT or MR angiogram of the neck vessels, which help to establish the presence of carotid or vertebral artery dissection and magnetic resonance venography (MRV), which is useful when evaluating possible cerebral venous sinus thrombosis [23].

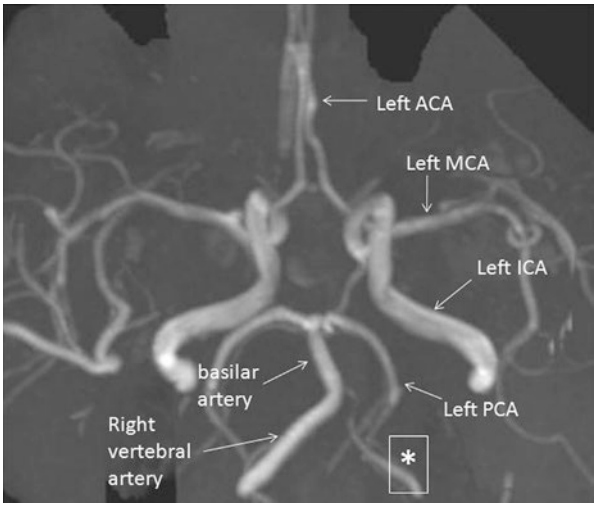

Fig. 21.8 MRA of the cerebral vasculature. Note the dominance of the right vertebral artery over left vertebral artery (*) in this patient (normal variant). ACA anterior cerebral artery, ICA internal carotid artery, MCA middle cerebral artery, PCA posterior cerebral artery

CT Perfusion (CTP)

CTP utilizes contrast-enhanced head CT to measure cerebral blood flow. This allows delineation between the ischemic penumbra (which is potentially salvageable) and the ischemic core (which is infarcted and therefore unsalvageable) [24]. CTP is most often used to determine whether a patient is a candidate for mechanical thrombectomy due to stroke from large artery occlusion.

Selecting Imaging Studies

Each stroke center has specific protocols for neuroimaging which are based, to some degree, on the preferences of the local stroke specialists and availability of interventional techniques. If rapid results to exclude hemorrhage are required to determine whether a patient is eligible for intravenous thrombolysis, then treatment should not be delayed, and a non-contrast head CT to exclude hemorrhage is the necessary and sufficient imaging study. However, if a high-sensitivity study is required to establish the diagnosis of stroke, MRI including DWI, ADC map, and susceptibility images is preferred. Vascular imaging studies including CTP help to define the pathophysiology of stroke and may be necessary if mechanical thrombectomy is planned.

Hyperacute Ischemic Stroke Treatment

Intravenous Recombinant Tissue Plasminogen Activator (rt-PA)

Intravenous recombinant tissue plasminogen activator (IV rt-PA) is a thrombolytic agent used to treat acute ischemic stroke. The dose of IV rt-PA is 0.9 mg/kg, with 10% given as a bolus and the remaining 90% infused over 1 hour. The total dose should not be greater than 90 mg.

IV rt-PA is effective when it is given within 4.5 hours of ischemic stroke onset [25–30]. While this may seem like a generous amount of time to make a decision and administer the medication, only a minority of eligible patients undergo thrombolysis because of delays in recognizing stroke, in getting to the emergency room in a timely fashion, in undergoing a directed history and non-contrast head CT, and in excluding contraindications to IV rt-PA. Thus, each minute spent in patient evaluation is critical, and it becomes essential to focus on the following questions to maximize the chance that a patient receives treatment:

1. When did the problem begin?
   IV rt-PA is beneficial for strokes treated within 4.5 hours of symptom onset. It is, therefore, imperative to establish the exact time at which deficits developed. Although initial investigations into IV rt-PA for patients who awaken with stroke seem promising, awakening with stroke is currently an exclusion from undergoing intravenous thrombolysis [31].
2. Is the deficit disabling?
   It is also necessary to establish that the deficit from the suspected ischemic stroke is disabling. Mild dysarthria or subtle non-dominant hand weakness probably do not warrant treatment with IV rt-PA, but hemiparesis, aphasia, or neglect do. However, there has been a trend towards treating patients with milder deficits with IV rt-PA based on the rationale that strokes may progress after presentation and that the likelihood of progression is not known a *priori* [32].
3. Is there an explanation for the neurologic deficit other than acute ischemic stroke?
   Hemorrhagic stroke is the most important condition that must be differentiated from acute ischemic stroke. All patients must undergo a non-contrast head CT prior to intravenous thrombolysis. CT will also help to exclude mass lesions which may mimic an ischemic stroke. Other important stroke mimics, including hypoglycemia, hyperglycemia, and postictal paralysis, are discussed in greater detail above.
4. Are there any contraindications to administering rt-PA?
   A set of contraindications to rt-PA is found in Table 21.3 [33].

The main serious side effect of rt-PA is intracranial hemorrhage, which occurs in up to 6% of patients who receive the medication [25]. Orolingual angioedema is another serious potential side effect that occurs in a small percentage of patients who have received rt-PA and requires treatment with antihistamines, steroids, and epinephrine [32].

Patients who receive rt-PA should be admitted to an ICU for close vital sign monitoring and serial neurological examinations for at least 24 hours. For IV rt-PA candidates with systolic blood pressure >185 or diastolic blood pressure >110 mm Hg, use antihypertensive medications such as labetalol (10–20 mg IV PRN) or nicardipine (5–15 mg per hour IV infusion) to lower the blood pressure. Anticoagulants and invasive procedures such as intravenous line and nasogastric tube placement should be avoided for 24 hours. CT scan should be performed 24 hours after rt-PA administration.

Should the patient develop any change in neurologic status, perform a CT scan immediately to exclude the possibility of hemorrhage. If a hemorrhage is detected,

Table 21.3 Contraindications to intravenous rt-PA

Recent history of intracranial hemorrhage
Intracranial hemorrhage on CT or MRI
History of stroke or serious head trauma within prior 3 months
Frank CT hypodensity involving >1/3 of the MCA territory
Brain surgery within 3 months
Known intra-axial brain tumor
Known or suspected infective endocarditis
Known or suspected aortic arch dissection
Active internal bleeding or recent gastrointestinal bleeding
Known bleeding diathesis
Persistent systolic blood pressure greater than 185 mm Hg or persistent diastolic blood pressure greater than 110 mm Hg
Platelets < 100,000
INR > 1.7
Heparin use with elevated PTT
Low-molecular weight heparin within previous 24 hours
Direct thrombin or factor X inhibitor use

then the patient should receive 10 units cryoprecipitate IV and tranexamic acid 1000 mg IV or aminocaproic acid 4–5 g until bleeding is controlled. Hematology and neurosurgical consultations should be obtained [32].

Mechanical Thrombectomy

Despite public education campaigns and community outreach programs, most patients with acute ischemic stroke will not reach a stroke center within the 4.5-hour window to receive IV rt-PA. Patients with large artery occlusions who arrive up to 6 hours after onset of new stroke deficits may be candidates for mechanical thrombectomy [34]. Those who arrive between 6 and 24 hours after stroke onset may be candidates for mechanical thrombectomy provided that they have a mismatch between the ischemic core and penumbra proven by a perfusion study [35, 36]. Patients who wake up with ischemic stroke and who are excluded from receiving IV rt-PA are included in this latter group.

Acute Antiplatelet Therapy

Aspirin 162-325 mg should be given to all patients with ischemic stroke who are not being treated with rt-PA within 24–48 hours of stroke onset [37]. In those who have been treated with rt-PA, aspirin should be given at the 24-hour mark, provided that there is no clinical concern or radiographic evidence for hemorrhage.

Acute Anticoagulation

The rationale for acutely anticoagulating a patient with acute ischemic stroke is that it may reduce the chance of early stroke recurrence, limit the extent of an existing stroke, and improve neurologic outcome. There is no clear evidence, however, that heparin or low-molecular weight heparin is effective in doing any of these things. In addition, these anticoagulants increase the risk of hemorrhagic stroke transformation or bleeding in other parts of the body. Until clear evidence is available that anticoagulation provides more benefit than risk, it is best to avoid heparin in patients

with acute ischemic stroke. Exceptions to this general statement include strokes due to arterial dissection, intracardiac thrombi, and venous sinus thrombosis, which are discussed below [38].

Blood Pressure Management

Blood pressure is almost always elevated in patients with acute ischemic stroke. Based on their experience with cardiac patients, non-neurologists often administer antihypertensive agents to stroke patients prior to requesting neurologic consultation. This approach is often harmful, as rapid blood pressure lowering may lead to hypoperfusion of the vulnerable ischemic penumbra and worsen both acute clinical signs and long-term outcome [39]. The indications for treating elevated blood pressure include [38]:

- Intravenous thrombolysis
- Excessive hypertension, arbitrarily defined as systolic blood pressure greater than 220 mm Hg or diastolic blood pressure greater than 120 mm Hg
- Signs of malignant hypertension such as retinal hemorrhages and exudates, acute renal failure, and hypertensive encephalopathy
- Evidence of compromise of other organ systems including cardiac ischemia or pulmonary edema

Labetalol (10–20 mg IV) is the most commonly employed antihypertensive agent for patients with acute ischemic stroke. In most cases, patients benefit from a slightly elevated cerebral perfusion pressure which may be achieved by lowering the head of the bed. Patients with perfusion-sensitive strokes may require intravenous pressors to keep their blood pressure elevated.

Surgical Treatment of Ischemic Stroke

Surgical treatment of ischemic stroke may be considered for the malignant MCA syndrome and cerebellar infarction.

Malignant MCA Syndrome

Large MCA infarctions, defined as those which involve more than 50% of the territory of the MCA, are associated with massive edema 24–48 hours after stroke onset and a high likelihood of death or poor neurological outcome [40]. Medical interventions targeted towards reducing swelling and lowering intracranial pressure are generally ineffective in changing the clinical course (Chap. 2). Decompressive hemicraniectomy, however, allows room for the swollen brain to expand, thereby reducing the probability of herniation and death. Although surgical intervention reduces the likelihood of poor outcomes, most surviving patients still need assistance with all their activities of daily living and will be unable to walk [41]. Decisions about surgical intervention should therefore be made carefully in conjunction with the patient's family, incorporating the patients' known prior wishes.

Cerebellar Infarction

Many patients with isolated cerebellar infarctions recover spontaneously and have no lasting stroke deficits. Other patients, particularly those with large SCA or PICA infarctions, develop massive edema 24–48 hours after stroke onset, leading to brainstem compression and obstructive hydrocephalus. A patient with a cerebellar infarction should be monitored frequently, and any change in their level of consciousness should prompt neurosurgical consultation. Suboccipital decompressive craniectomy may reduce the likelihood of death and poor neurologic outcome, and many patients who undergo surgery survive with only modest deficits. Because surgical intervention is widely considered the standard of care in rapidly progressing cerebellar infarction, a randomized controlled trial to define the exact benefit of surgery is unlikely.

Inpatient Evaluation

Cardiac Evaluation

Atrial fibrillation (AF) and intracardiac thrombi are important sources of embolic strokes. Evaluation for AF and thrombi begins with careful cardiac auscultation to screen for irregular rhythms or murmurs. Cardiac telemetry should be ordered for at least 24 hours to attempt to detect atrial fibrillation, though mobile monitoring for 21 days or longer increases the diagnostic yield [27, 42]. Consider using an implantable loop recorder to maximize the chance of detecting atrial fibrillation in patients with potential embolic strokes [43].

Transthoracic echocardiography (TTE) is usually the first test to evaluate for a structural cardiac abnormality in patients with stroke. Transesophageal echocardiography (TEE) is superior to TTE for detecting abnormalities such as left atrial appendage thrombi, aortic atheromatous disease, patent foramen ovale (PFO), and atrial septal aneurysms [44]. Lower extremity Doppler studies should be ordered for patients with PFO to investigate for a source of paradoxical embolism.

Vascular Evaluation

Head MRA or CTA are typically performed at initial presentation of stroke to assess for intracranial stenosis and evaluate for possibly thrombectomy candidacy. Neck MRA or CTA are useful for evaluating potential cervical carotid and vertebral artery dissections. Imaging of the extracranial carotid arteries to evaluate for carotid artery stenosis is generally performed on the first day after a stroke and not in the hyperacute setting:

- Conventional angiography. While conventional angiography is the gold standard for the assessment of carotid artery stenosis, it is an invasive procedure associated with a 1% risk of adverse events including death and disabling stroke [45]. Many vascular surgeons, however, still prefer to perform conventional angiography to accurately define vascular anatomy when planning carotid intervention.

- Carotid duplex ultrasound. This study is noninvasive and does not pose any risks of radiation or contrast dye exposure.
- CT and MR angiography. Because ultrasound may overestimate the degree of carotid artery stenosis, MRA (with fat-suppressed images) or CTA of the neck vessels often play a confirmatory role. For patients with posterior circulation strokes, MRA or CTA of the cervical portion of the vertebral arteries are used to evaluate suspected vertebral artery dissections.

Blood Tests

Because hyperlipidemia and diabetes are common modifiable risk factors for stroke recurrence, lipid levels and hemoglobin A_{1c} percentages should be measured in all patients with ischemic stroke. Blood tests for hypercoagulable states are ordered excessively and often incorrectly in stroke patients. Testing for deficiencies of protein C, protein S, antithrombin III, plasminogen, activated protein C resistance/factor V Leiden mutation, anticardiolipin antibodies, and lupus anticoagulant is generally of low yield [46]. All of these abnormalities increase the risk for venous thromboembolism, but only lupus anticoagulant predisposes to both arterial and venous thromboembolism. Patient factors that may increase the yield of hypercoagulability testing include age <50, prior venous thrombosis, multiple family members with venous thrombosis, and personal history of miscarriages. Because recent stroke, heparin, and warfarin reduce the sensitivity of hypercoagulable factor testing, it is advisable to test a patient at least 2 months after their stroke and to discontinue any anticoagulants at least 2 weeks prior to testing.

Uncommon Causes of Stroke

Most strokes are secondary to hypertension, atherosclerosis, and atrial fibrillation. Less common but important causes of stroke should be considered in the presence of systemic signs or symptoms or in special populations such as pregnant women and young patients. A review of these causes is beyond the scope of this text, but vasculitides, connective tissue disorders, angiopathies, metabolic disorders, substances of abuse, and infections should be considered when obvious stroke risk factors are absent.

Secondary Prevention

Minimizing the chance of stroke recurrence is a critical goal of stroke treatment. Time is of the essence when planning a protocol for secondary prevention, especially in patients with TIA, as the risk of a completed stroke is particularly high in the very early period, approximately 5% in the first week [47].

Antiplatelet Agents

Antiplatelet agents are used as secondary stroke prophylaxis for most patients who have had ischemic strokes. Aspirin 81 mg qd is the most common agent used for long-term stroke prophylaxis. Clopidogrel 75 mg qd is as effective as aspirin and would be an option for patients who have allergy to or intolerance of aspirin [48].

For patients with stroke due to intracranial atherosclerosis, dual antiplatelet therapy with aspirin 325 mg qd and clopidogrel 75 mg qd for 90 days followed by aspirin monotherapy may be superior to either medication alone [49].

The combination of aspirin and dipyridamole (25/200 mg bid) is more effective than aspirin alone and as effective as clopidogrel in stroke prophylaxis [50–52]. Its use is limited by expense and intolerance due to headache.

Anticoagulation

Patients with stroke secondary to atrial fibrillation traditionally were treated with warfarin, aiming for a goal INR of 2.0–3.0 [53]. Direct oral anticoagulants including the factor X inhibitors apixaban (5 mg bid) and rivaroxaban (20 mg qd) and the direct thrombin inhibitor dabigatran (150 mg bid) have largely supplanted warfarin due to greater safety and ease of use [54–57]. Their main disadvantages of these newer agents are expense and the lack of laboratory monitoring to measure compliance and effectiveness.

Only a few stroke etiologies beyond atrial fibrillation require oral anticoagulation for secondary stroke prophylaxis:

- Consider anticoagulation for patients with hypercoagulable states or cerebral venous sinus thrombosis for 3–6 months.
- Consider anticoagulation for patients with cervical carotid or vertebral artery dissections, keeping in mind that there is no clear benefit of anticoagulation compared to antiplatelet therapy [58].
- There is no clear evidence supporting anticoagulation for patients with patent foramen ovale (PFO), atrial septal aneurysm (ASA), or the combination of PFO and ASA [59, 60].
- Anticoagulation is not recommended for patients with ischemic stroke of undefined etiology (cryptogenic strokes), including strokes which appear to have presumed but not confirmed embolic origin [61–63].

Blood Pressure Control

In the acute setting, lowering blood pressure is often harmful to a patient with an ischemic stroke as it may decrease perfusion to vulnerable areas of the brain. For secondary prevention, however, hypertension is the most commonly identified

treatable stroke risk factor. Blood pressure treatment (for patients without hypertensive emergencies, in whom immediate treatment is required) may begin safely at 24 hours after stroke onset [27]. It may be more appropriate to wait 72 hours for patients with lacunar infarctions, as these patients may be more susceptible to deterioration should hypotension occur. Although specific target blood pressure levels are not defined, a systolic blood pressure of less than 130 decreases the likelihood of stroke recurrence [64]. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and diuretics are all treatment options. Choice of specific agents for blood pressure control is based on patient tolerance, other medical conditions, and medication expense.

Hyperlipidemia

Statins (3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors) reduce the risk of stroke recurrence by approximately 20% and should be prescribed for patients with low-density lipoprotein levels greater than 100 mg/dL [65]. Patients with normal LDL and total cholesterol levels also benefit from statin therapy [66]. Although the majority of stroke risk reduction is likely secondary to lowering of LDL levels, other important effects of statins include plaque stabilization and anti-inflammatory actions. Diet and other agents capable of lowering cholesterol are not as effective as statins in secondary stroke prevention [67]. Thus, all patients with ischemic stroke should be treated with atorvastatin 40–80 mg qd, lovastatin 40 mg qd, pravastatin 40 mg qd, simvastatin 40 mg qd, or rosuvastatin 10 mg qd as tolerated. Side effects of these medications include myotoxicity (Chap. 10), diarrhea, and transaminitis.

Ezetimibe (10 mg qd), which works by inhibiting cholesterol absorption and metabolism, may be an option for secondary stroke intervention in patients with hyperlipidemia who are intolerant of statins [68].

Diabetes Mellitus

Diabetes mellitus is an independent risk factor for ischemic stroke. Strict glucose control (hemoglobin A_{1c}% less than 7%), whether achieved by diet, oral hypoglycemic medications, or aggressive insulin therapy, decreases the risk of stroke recurrence [53].

General Lifestyle Recommendations

While published BMI goals for stroke patients are not available, it is important to recommend weight loss, as overweight patients (BMI > 25 kg/m^2) are at increased risk for stroke recurrence. It is also important to encourage smoking cessation and regular exercise.

Carotid Endarterectomy and Stenting

Symptomatic Carotid Artery Stenosis

As discussed above, carotid artery stenosis is an important cause of stroke and transient ischemic attacks. Carotid endarterectomy (CEA) is the standard surgical approach to prevent ipsilateral stroke or transient ischemic attack from carotid artery stenosis. The most important variable in determining who should undergo CEA is the degree of carotid stenosis:

- Patients with stenosis between 70% and 99% derive the greatest benefit from CEA and should undergo surgery, preferably within 2 weeks of their stroke or transient ischemic attack [69–71]. Patients with very large infarctions or those whose strokes have already undergone hemorrhagic transformation may benefit from waiting longer than 2 weeks before intervention.
- Patients with 50–69% stenosis may or may not benefit from surgery. Men with this degree of stenosis tend to benefit more from CEA than women do [72]. To improve the chances of a good outcome, CEA for 50–69% stenosis should only be performed by surgeons with low complication rates.
- Patients with stenosis less than 50% or complete occlusion of the carotid artery should be managed with antiplatelet agents and statins.

Carotid artery stenting is a less invasive interventional approach to carotid artery stenosis which may be appropriate for patients who have multiple medical comorbidities, extensive or poorly accessible lesions, radiation-induced carotid stenosis, and restenosis after previous CEA [73]. The benefit of carotid artery stenting is similar to the benefit of CEA, though CAS is more likely to produce complications in patients who are older than 70 [74, 75].

Asymptomatic Carotid Artery Stenosis

Carotid bruits are detected frequently on routine physical examination. Primary care physicians often refer these patients to neurologists or do so after a vascular imaging study discloses carotid artery stenosis. In some cases, vascular surgeons seek guidance in managing these patients. Meta-analysis of the three major studies which addressed surgical treatment showed that carotid endarterectomy for patients with moderate-to-severe stenosis (defined as 60–99% in two of the studies and 50–99% in the third) reduced the absolute risk for stroke by approximately 1% for each year of subsequent survival [76]. The benefit of carotid endarterectomy was counterbalanced by a perioperative risk of stroke or death of approximately 3%. Benefits of intervention appeared to be greater for men than for women. It is reasonable, therefore, to consider CEA or CAS for patients with asymptomatic carotid stenosis on a case-by-case basis.

Other Interventions

Patent foramen ovale (PFO) is noted frequently on echocardiogram, but its direct relevance to a specific stroke patient is often unclear. Percutaneous PFO closure may be considered for younger patients without traditional risk factors for stroke [77–79].

Stenting of the vertebral artery may be an option for rare patients with continued symptomatic posterior circulation ischemia despite maximal medical treatment [80].

Supportive Care

Although supportive measures often take a back seat to thrombolysis decisions and antiplatelet agent selection, they are critical in reducing disability and death from stroke. The pillars of supportive care for stroke patients are:

Treating Hyperthermia and Infection

Hyperthermia worsens stroke outcome, independent of the presence of underlying infection [81]. Evaluate for sources of fever by performing a complete blood count, blood cultures, chest X-ray, urinalysis, and urine cultures. Treat with antibiotics if a relevant infection is identified. For patients with unexplained fevers, consider lower extremity duplex ultrasound studies to investigate for deep venous thrombosis, echocardiography to evaluate for endocarditis, and infectious disease consultation. Treat mild hyperthermia with antipyretics such as acetaminophen and more severe hyperthermia with antipyretics and cooling blankets.

Correcting Hyperglycemia

Because hyperglycemia, like fever, worsens stroke outcome, it is important to maintain strict glucose control [82].

Maintaining Adequate Nutrition

Dysphagia, weakness, and cognitive impairments all lead to inadequate nutrition and impede recovery from stroke. If necessary, prescribe parenteral nutrition or tube feedings. Do not use hypotonic fluids, as they may worsen brain edema.

Assessing Aspiration Risk and Preventing Aspiration

Patients with strokes involving large hemispheric territories or the brainstem are at increased risk for aspiration which may lead to both acute airway compromise and aspiration pneumonia. Assess aspiration risk at the bedside by asking the patient to swallow three ounces of water and then observing for coughing or a wet, hoarse voice [83]. A patient who fails this simple swallow test is at risk for aspiration and should be placed on precautions which may include monitored eating or restrictions on oral intake. Because difficulties may be subtle (e.g., silent aspiration), patients often require a formal swallowing study to determine whether dysphagia is present.

Deep Venous Thrombosis (DVT) Prophylaxis

Patients with severe stroke deficits may be bedbound for several days or longer, making DVT prophylaxis essential to preventing life-threatening pulmonary emboli. Unless there is a clear contraindication (such as heparin-induced thrombocytopenia or a bleeding diathesis), DVT prophylaxis should consist of unfractionated heparin (5000 units sc tid) or a low-molecular weight heparin [38]. Treat patients who cannot receive heparin with sequential compression devices.

Preventing Falls

Weakness, ataxia, sensory impairments, and cognitive dysfunction are all factors which increase the risk of falls following stroke. Activating bed alarms, employing patient sitters, or even using physical restraints may be necessary to prevent falls and additional injuries.

Initiating a Rehabilitation Program

Recovery from stroke is a complex process that results from a combination of brain adaptation to injury by neural repair and by patient-driven efforts to compensate for irreparable deficits. Improvement is usually maximal within 3–6 months of a stroke [84]. Cognitive deficits including aphasia may have a longer window for recovery than motor deficits do. Early rehabilitation tends to be more effective than delayed rehabilitation, and for this reason, it is important to involve physical therapists, occupational therapists, speech and swallowing specialists, and cognitive rehabilitation experts as soon as possible [85].

Evaluation and Treatment of Intracranial Hemorrhage

Intracranial hemorrhage (ICH) is a life-threatening emergency associated with high morbidity and mortality. It may be difficult to differentiate ICH from ischemic stroke on clinical grounds alone. As noted above, possible clues to ICH include headache and the presence of deficits which progress over minutes to hours. Emergency room physicians or other doctors usually make the diagnosis of ICH by non-contrast head CT, well before a neurologist is involved.

Acute Life Support

Because a patient with ICH may present in extremis, the first priority is to assure that they have a patent airway, adequate cardiopulmonary function, and intravenous access for medication administration. A patient with ICH may be initially conscious and then deteriorate rapidly. Thus, it is essential to monitor the patient carefully and transfer them to an intensive care unit should their clinical condition decline.

Reversing Anticoagulation

After ensuring basic life support measures, the next step in managing ICH is to discontinue any anticoagulants and reverse their effects if possible. Review the patient's medication list and check their prothrombin time, partial thromboplastin time, and platelet count.

Warfarin

The three options available for reversing anticoagulation secondary to warfarin are:

- Fresh frozen plasma (FFP) 15–20 mL/kg. FFP is widely available, but administration may be delayed by thawing and preparation. FFP requires a relatively large volume of administration and may precipitate or worsen congestive heart failure.
- Prothrombin complex concentrate (PCC, factor IX complex) 25–50 IU/kg. PCC reverses the blood-thinning effects of warfarin within several hours, but because of its short half-life, it must be accompanied by vitamin K. It does not require blood type matching and can be prepared in minutes because it is reconstituted at room temperature. The volume of infusion required is much smaller than for FFP, which makes it more attractive for patients at risk for congestive heart failure. Compared to FFP, anticoagulation reversal and the rate of serious side effects including death are lower in patients treated with PCC [86].
- Vitamin K 10 mg IV. Treat all patients with symptomatic ICH who are taking warfarin with vitamin K. Because vitamin K requires at least 24 hours to work, it is not appropriate monotherapy for reversing ICH in the hyperacute setting.

Heparin

Reverse heparin using protamine sulfate. In general, the dose of protamine is 1 mg per 100 units of heparin if the heparin is being actively infused and between 0.25 and 0.5 mg per 100 units if the heparin was discontinued more than 30 minutes prior to beginning protamine infusion. It is good practice to review each case with a pharmacist in order to optimize treatment.

Direct Oral Anticoagulants

Dabigatran can be reversed using idarucizumab (2.5 g × 2 doses) [87]. Beyond stopping the relevant medication, there is no pharmacological method to reverse the anticoagulant effects of apixaban or rivaroxaban. In addition, there is no laboratory monitoring that can track the degree of anticoagulation with these agents, so the success of anticoagulation reversal must be assessed by observing the clinical examination and serial CT scans.

Blood Pressure Treatment

Blood pressure management in acute ICH is an area of great controversy. Lowering blood pressure reduces the likelihood of hemorrhagic expansion but may also lower perfusion pressure and increase the risk for perilesional ischemia. Similar to ischemic stroke, there is no clearly defined ideal blood pressure. Published guidelines suggest a goal blood pressure of no greater than 160/90 for ICH patients, but it is not clear that aggressive blood pressure reduction in the acute setting leads to an improvement in long-term outcomes [88, 89]. The agents used most commonly to lower blood pressure in ICH are labetalol (10–20 mg IV) and hydralazine (5–10 mg IV) by intravenous push.

Managing Increased Intracranial Pressure

Intraparenchymal hemorrhage may result in increased intracranial pressure, a potentially life-threatening emergency which is discussed in further detail in Chap. 2.

Surgical Intervention

Surgical hematoma evacuation has the theoretical potential to rescue vulnerable adjacent brain tissue from ischemia and to reduce the likelihood that ICH will increase intracranial pressure and cause herniation. Despite these possible benefits,

decompressive craniectomy does not appear to improve neurologic outcomes or reduce the chance of death in most patients with supratentorial ICH [88]. Large cerebellar hemorrhages (>3 cm), however, may produce brainstem compression and obstructive hydrocephalus and should be evacuated as soon as possible to prevent further neurologic deterioration [90].

External ventricular drains may be beneficial for patients with intracerebral hemorrhage with intraventricular extension and hydrocephalus [91]. The benefit of intraventricular thrombolysis is not clear [91].

Defining ICH Etiology

Defining the etiology of ICH helps to prevent hemorrhage recurrence and points to underlying disease processes that may need specific therapies. Common causes of ICH include:

- Hypertension. This is the most common cause of ICH. Typical locations of hypertensive hemorrhages include the caudate nucleus, thalamus, pons, and cerebellum.
- Amyloid angiopathy. Hemorrhages secondary to amyloid angiopathy tend to involve the parietal and occipital lobes. Other than location, finding cerebral microbleeds with susceptibility imaging studies may help to identify amyloid angiopathy as the source of ICH (Fig. 21.7).
- Anticoagulant and thrombolytic agents.
- Bleeding diatheses such as hemophilia and von Willebrand disease. In most cases, these conditions are identified long before ICH occurs.
- Metastatic tumors. Tumors that have a propensity to bleed include renal cell carcinoma, melanoma, thyroid carcinoma, and choriocarcinoma. In patients with a known primary cancer, defining metastasis as the etiology is often straightforward. In patients with no known primary tumor, a careful screening examination must be conducted, as discussed in Chap. 23.
- Arteriovenous malformations. These should be considered as an etiology of ICH in younger patients. Although these masses have a characteristic appearance, they may be masked by the overlying hemorrhage. Arteriovenous malformations are discussed further in Chap. 23.

Prognosis of Intracranial Hemorrhage

Approximately half of patients with ICH will die within 30 days [92, 93]. The most important prognostic factors are the initial level of consciousness as defined by the Glasgow Coma Scale in Table 21.4 and volume of the hemorrhage, which can be estimated from the CT scan using the formula [93, 94]:

Table 21.4 Glasgow Coma Scale

Parameter	Best response	Points
Eye movements	Opens eyes spontaneously	4
	Opens eyes in response to voice	3
	Opens eyes in response to painful stimuli	2
	Does not open eyes	1
Verbal response	Appropriate conversation	5
	Disoriented	4
	Utters inappropriate words	3
	Groans incomprehensibly	2
	No verbal response	1
Motor response	Obeys commands	6
	Localizes painful stimuli	5
	Withdrawal to painful stimuli	4
	Decorticate posturing	3
	Decerebrate posturing	2
	No movement	1

Glasgow Coma Scale (GCS) is derived by adding the best eye movement, verbal response, and motor response

$$\text{Volume} = \frac{A \times B \times C}{2}$$

where

A = the largest diameter of the hemorrhage

B = the diameter perpendicular to the hemorrhage

C = the number of slices occupied by the hemorrhage on the CT scan multiplied by the slice thickness

In one study, patients with ICH volumes greater than 60 cm^3 and GCS scores less than or equal to 8 had a 30-day mortality of 91%, while those with a volume less than 30 cm^3 and GCS scores greater than 8 had a 30-day mortality of 19% [93]. Other risk factors for poor ICH outcome include older age, intraventricular blood, early clinical deterioration, infratentorial hemorrhage location, and hematoma growth on serial CT scans [95].

Restarting Anticoagulation After Intracerebral Hemorrhage

In many cases, intracerebral hemorrhage is a direct consequence of anticoagulation for atrial fibrillation or a hypercoagulable state. While discontinuing anticoagulants in the acute setting is necessary to prevent hemorrhage expansion, restarting these medications after the hemorrhage has resolved is usually necessary. The annual rate of hemorrhage recurrence in patients who have resumed oral anticoagulation is approximately 2.5%, though this is likely an underestimate, as the study from which this number is derived excluded patients with severe hemorrhages [96]. The optimal timing for restarting anticoagulation is not clear: published time frames range from intervals as short as 3 days to as long as 30 weeks [97, 98]. In the absence of

high-quality evidence, decisions about whether to restart anticoagulants and the timing of doing so must be highly individualized.

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Multiple Sclerosis

22

Clinically Isolated Syndromes (CIS) Suggestive of Multiple Sclerosis

CIS is the most common initial presentation of MS. It is usually due to a single lesion or multiple simultaneous lesions of the central nervous system, though a thorough history may reveal prior events that suggest MS. Examples of CIS include:

Visual Loss

Optic neuritis is one of the most common presentations of MS (see also Chap. 5). Typically, this condition is characterized by unilateral visual loss and a tugging retrobulbar pain which develops over several days. Eye movements and bright lights may exacerbate the eye pain. Visual acuity may be decreased to any degree, and color vision is often affected out of proportion to other vision modalities. A relative afferent pupillary defect is present in the affected eye. Ophthalmoscopic examination is usually normal at presentation, as most patients have retrobulbar optic neuritis.

Myelopathy

Transverse myelitis is an inflammatory disorder of the white matter of the spinal cord that produces acute or subacute weakness, sensory loss, gait impairment, and urinary incontinence. The transverse myelitis most typical of MS is usually a partial myelopathy rather than a dense paraplegia (Chap. 17). A thoracic banding sensation, in which the patient describes tightness around the thoracic region, may occur. A sharp sensory level is not typical.

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Sensory Syndromes

A variety of sensory syndromes may herald the onset of MS. Typical symptoms include numbness and a perception of abnormal vibration, or of pins and needles. Sharp, burning pains are a less common presenting symptom. Common locations of sensory system involvement include a single limb, both legs simultaneously, a band around the thorax, and in the distribution of the trigeminal nerve. Trigeminal neuralgia in a young person, especially when associated with trigeminal sensory loss, suggests MS. Lhermitte's symptom occurs when forward flexion of the neck leads to an abnormal electrical sensation shooting down the back. It is secondary to cervical spinal cord lesions, especially MS, but is not pathognomonic for the disease.

Motor Syndromes

Focal weakness is another common initial MS presentation. A lesion in the subcortical white matter or brainstem may produce weakness of the contralateral face, arm, or leg. Pontine lesions may lead to ipsilateral facial weakness which mimics Bell's palsy. Patchy spinal cord lesions may result in ipsilateral monoparesis. Transverse myelitis, as noted above, may cause bilateral leg weakness.

Diplopia

The classical pattern of diplopia in MS is internuclear ophthalmoplegia (INO) in which a lesion of the medial longitudinal fasciculus disconnects the contralateral abducens nucleus in the pons from the ipsilateral oculomotor nucleus in the midbrain (Chap. 6). Abduction of the contralateral eye is normal, while adduction of the ipsilateral eye is impaired. When INO occurs in MS, it is often bilateral. Other brainstem lesions may produce horizontal, vertical, or oblique diplopia. Because brainstem disease in MS may be multifocal, diplopia in MS is often difficult to pinpoint.

Incoordination

Demyelination involving the cerebellar white matter and its brainstem connections, particularly the middle cerebellar peduncle, may lead to incoordination and ataxia. This is often accompanied by severe action or intention tremor.

Multifocal and Progressive Presentations

Approximately 20% of the time, MS presents with dysfunction at more than one level of the nervous system [1]. Patients with multifocal presentations may be

dismissed as having psychogenic disease because of the great variety of their symptoms. MS is progressive from onset rather than relapsing in approximately 15% of patients [1].

The Radiologically Isolated Syndrome

The use of MRI to evaluate patients with headaches and other soft neurologic complaints is widespread and growing. T2-weighted hyperintensities are common findings on these MRI, and many asymptomatic patients with these nonspecific lesions are referred to neurologists for MS evaluations. Some patients, however, have radiographically typical MS lesions (see below) without a history of clinical symptoms suggestive of MS and may be labeled as having "radiologically isolated syndromes." Because these patients have up to a 33% chance of developing a CIS or MS, they should be monitored closely for clinical symptoms of MS [2]. The presence of demyelinating lesions within the spinal cord increases the risk that a patient with a radiologically isolated syndrome will develop CIS or MS [3].

Atypical Symptoms

From an epidemiologic perspective, new MS is unlikely in patients older than 65 and uncommon even in those older than 50. Obvious peripheral nervous system dysfunction including dense distal sensory loss, sensory ataxia, areflexia, and bilateral hearing loss strongly suggests that MS is not the diagnosis. Complete transverse myelitis is uncommon in MS and points to other diagnoses including NMO spectrum disorders. Symptoms including dry eyes, dry mouth, rash, persistent fevers, and joint aches point to primary rheumatologic processes rather than to MS. Mental retardation or psychiatric dysfunction should prompt consideration of mitochondrial disorders, spinocerebellar ataxias, and the leukodystrophies. Strong family histories are uncommon in MS and suggest alternative diagnoses such as the spinocerebellar ataxias, the leukodystrophies, hereditary spastic paraplegia, or Leber hereditary optic neuropathy.

Making the Diagnosis

Early diagnosis is valuable because it allows disease-modifying therapy to be initiated at the beginning of the disease process. Unfortunately, there is no single symptom, sign, imaging finding, or laboratory test that is 100% reliable for diagnosing MS, and only 1/3 of patients referred for MS evaluation will actually have the diagnosis [4]. In many cases, these patients have functional neurologic disorders including somatic symptom disorder and conversion disorders. The diagnosis is only established by examining the clinical and laboratory data for evidence of demyelination separated in space and time (or for disability progressing over a year or more) and then excluding

conditions that imitate MS. In some cases, the diagnosis is established by history and physical examination. In most cases, adjunctive tests are necessary.

Past History

Inquire about prior symptoms typical for MS such as visual loss, weakness, numbness, double vision, vertigo, and clumsiness. Deficits which lasted longer than 24 hours support the diagnosis, while those which lasted only for several minutes or hours are less suggestive of MS. When reviewing the past history, ask about the evaluation that was performed at the time of each prior symptom, and review these results if available.

Physical Examination

Physical examination often discloses evidence of prior episodes of demyelination. Most useful among these are findings that suggest prior optic neuritis such as red desaturation, optic atrophy, and relative afferent pupillary defects (Chap. 5), or those that reflect demyelination of the spinal cord such as hyperreflexia and upgoing toes.

Magnetic Resonance Imaging

MRI of the brain and spinal cord are the most useful diagnostic studies for patients with suspected MS. As noted above, the diagnosis of MS hinges upon demonstrating central nervous system demyelination separated in both space and time, and MRI offers important information in both dimensions. Standard MS protocols should include T1, T2, FLAIR (in both the axial and sagittal planes), and contrast-enhanced T1 images of the brain. Patients with spinal presentations require T1, T2, and contrast-enhanced T1 images of the spine. A diagnosis of MS is highly unlikely when multiple imaging studies are normal.

T2 and FLAIR Imaging

The T2 hyperintense plaque is the characteristic MRI finding of demyelination secondary to MS (Fig. 22.1). Plaques are generally easier to visualize with FLAIR (fluid-attenuated inversion recovery), a sequence in which the bright CSF signal is removed. Common plaque locations are in the periventricular white matter, juxtacortical white matter, corpus callosum, and middle cerebellar peduncle. Although plaques may have a variety of appearances, those which are ovoid in shape are most suggestive of MS. Punctate lesions (<3 mm in size) are not considered reliable indicators of MS. Lesions in the corpus callosum which are oriented perpendicularly to the lateral ventricles are known as Dawson's fingers (Fig. 22.2) and are characteristic of

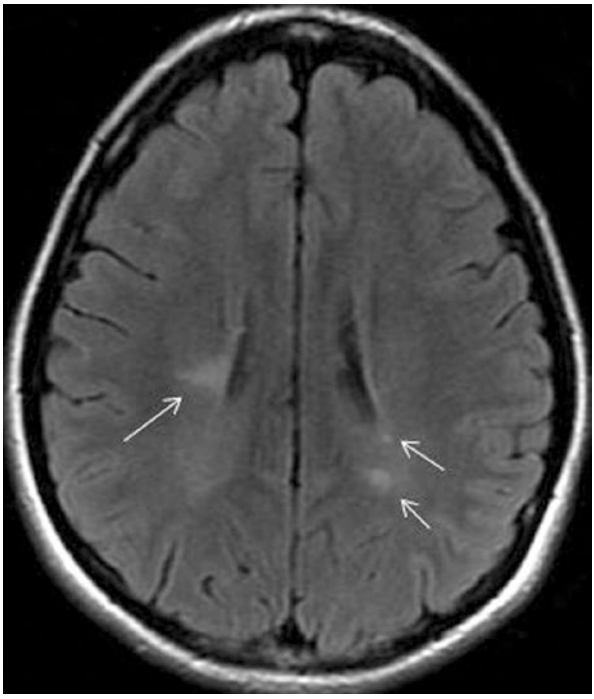

Fig. 22.1 Axial FLAIR MRI showing characteristic T2-hyperintense plaques in a patient with MS

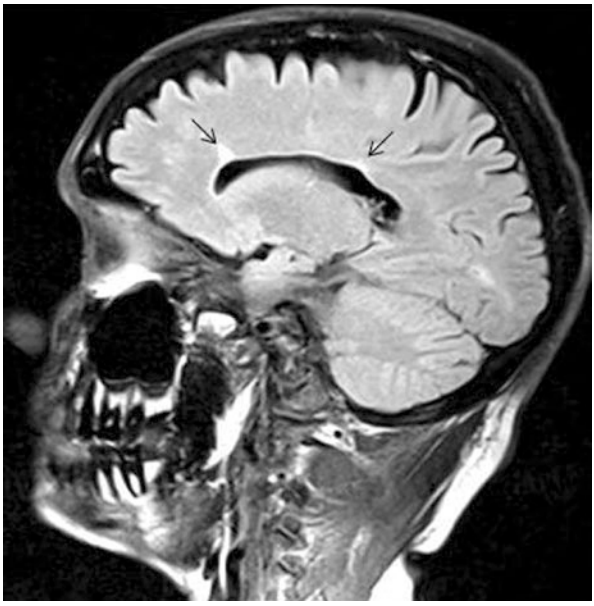

Fig. 22.2 Sagittal FLAIR MRI shows Dawson's fingers: two periventricular plaques oriented perpendicularly to the lateral ventricles, a finding highly characteristic of MS

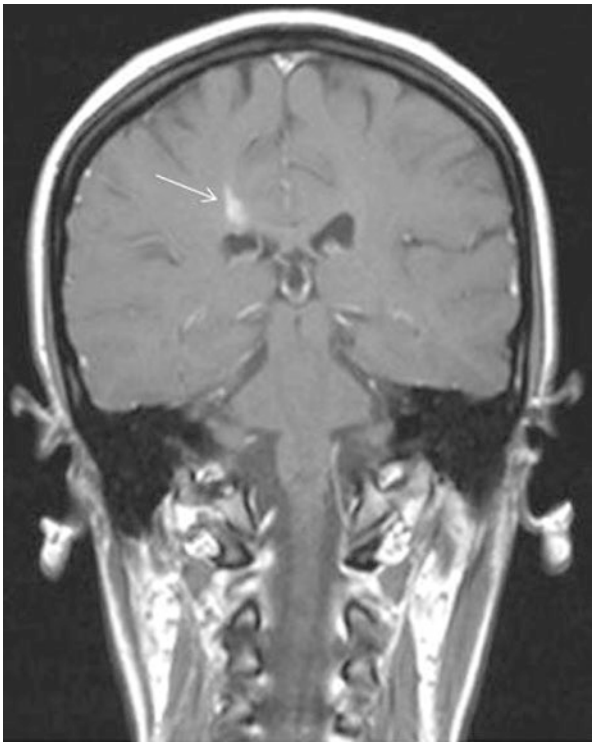

Fig. 22.3 Contrast-enhanced coronal MRI shows an enhancing lesion in a patient with relapsing-remitting MS

MS. These lesions are best visualized using FLAIR sequences in the sagittal plane. Plaques may accompany both new and old (presumably inactive) MS symptoms.

Contrast-Enhanced T1-Weighted Imaging

Gadolinium enhancement is used to detect active foci of blood-brain barrier disruption and therefore active MS (Fig. 22.3). Almost 75% of MS lesions will enhance for less than 1 month, and almost 95% will enhance for less than 2 months [5]. All findings must be correlated with the clinical history and examination, as new symptoms may not necessarily correlate with enhancing lesions and enhancing lesions may not be accompanied by new symptoms.

T1 Black Holes

Hypointense (dark) signals on T1-weighted images are thought to reflect prior demyelination and irreversible axon loss (Fig. 22.4) [6].

Spine MRI

Spine MRI with T1, T2, and contrast-enhanced sequences is especially important in patients presenting with transverse myelitis. It is also helpful in evaluating limb or trunk deficits that might not be explained by brain MRI and to add confidence to an

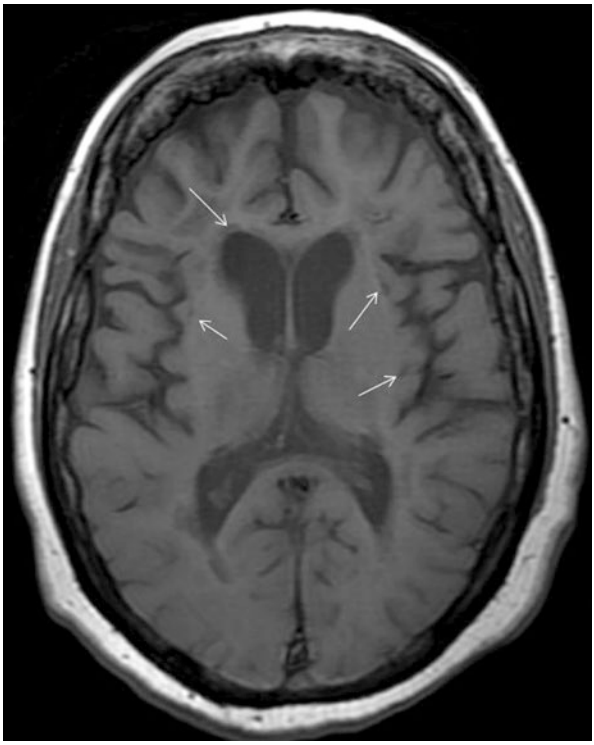

Fig. 22.4 T1 black holes in a patient with advanced MS. Note also the presence of cerebral atrophy

MS diagnosis in patients with equivocal brain lesions. Spine MRI lesions in MS involve the dorsal or lateral spinal cord rather than a dense transverse cross-section and are typically not longitudinally extensive.

Lumbar Puncture

Basic Studies

Cerebrospinal fluid abnormalities may support the diagnosis of MS and help to exclude imitators. The typical CSF profile in MS includes a mild elevation in lymphocytes (never exceeding 50 cells/mm^3) and a mildly elevated protein (less than 100 mg/dl). Neutrophilic predominance, very low glucose, and very high protein levels should prompt consideration of other diagnoses.

Oligoclonal Bands

Patients with MS synthesize abnormal IgG intrathecally. These antibodies can be separated using gel electrophoresis into oligoclonal bands (OCBs), preferably by using isoelectric focusing on agarose gels with immunoblotting: more than 95% of patients with MS will have positive OCBs [7]. When evaluating for OCBs, also perform serum protein electrophoresis to verify that the IgG is being synthesized

intrathecally. Finding elevated OCBs adds to the diagnostic certainty in patients with single MRI lesions and when there is no clear evidence of dissemination in time [8, 9]. OCBs may improve the specificity of an MS diagnosis when alternatives are being considered.

Visual Evoked Potentials (VEPs)

VEPs are the electrical potentials recorded from the scalp over the occipital lobes in response to visual stimuli. The typical protocol involves presenting an alternating checkerboard pattern to each eye in sequence and measuring the latency of the response recorded in the occipital cortex. Normally, this response has a positive deflection and a latency of approximately 100 msec and is thus called the P100 response. Patients with prior optic neuritis have prolonged or absent P100 responses recorded from the affected eye. In practice, an abnormal P100 is used to establish that there is a second lesion separated in space and time from the CIS that led to clinical presentation [10].

Patience

In most cases, MS is diagnosed by demonstrating clinical and radiographic white matter lesions separated in both space and time. Often, this is not possible at the initial encounter despite the most thorough history, examination, and set of laboratory and imaging studies. When the diagnosis remains in doubt, a comprehensive re-evaluation, including repetition of neuroimaging in 3–6 months or at a time when further symptoms develop, is usually the most appropriate approach.

Differential Diagnosis

Other Primary Demyelinating Disorders

Neuromyelitis Optica (NMO)

The core clinical features of NMO for which the disorder is named are optic neuritis and transverse myelitis. The optic neuritis and transverse myelitis may develop simultaneously, be separated by intervals of weeks or months, or even occur years apart [11]. The disorder usually has a relapsing course similar to MS, but may also be monophasic [11]. Several features help to differentiate between the two conditions:

- Optic neuritis NMO is usually bilateral, which is unusual for MS [12]. Radiographically, the optic neuritis lesions often involve more than half the length of the nerve, extending posteriorly into the optic chiasm. Incomplete recovery after an attack of optic neuritis is more likely in NMO than it is in MS.
- The myelopathy of NMO is much more severe and characteristically involves three or more consecutive segments ("longitudinally extensive transverse myelitis") with enlargement and later cavitation of the spinal cord, features that are all unusual in MS [13].

- Sparing of the brain both clinically and radiographically also favors a diagnosis of NMO rather than MS. Some patients with NMO, however, have abnormal brain MRI, occasionally resembling that found in MS [14, 15].
- Lesions of the area postrema are characteristic of NMO and may produce severe nausea and vomiting as the presenting clinical feature [16].
- CSF findings that are more consistent with NMO include a CSF neutrophilic pleocytosis during an attack and an absence of oligoclonal bands [11].

Approximately 75% of patients with NMO have antibodies to the aquaporin-4 water channel (also referred to as NMO-IgG) in the serum [17, 18]. Patients who are seronegative for NMO Ab may have antibodies to the myelin oligodendrocyte glycoprotein (MOG) [19].

Treat acute attacks of NMO with high-dose methylprednisolone 1000 mg qd × 3–5 days followed by a prednisone taper for 3–6 months. Plasmapheresis may help patients who do not show signs of a response within 1 week [20]. Options for maintenance therapies include azathioprine, methotrexate, mycophenolate mofetil, and rituximab [21]. Avoid disease-modifying agents used for MS such as interferons and natalizumab, as these have the potential to increase NMO activity [22].

Acute Disseminated Encephalomyelitis (ADEM)

This multifocal demyelinating disorder of the central nervous system usually develops several days or weeks after an infection or vaccination. ADEM symptoms are typically more severe and more numerous than MS symptoms. Cognitive changes, seizures, and even coma may occur in ADEM but are distinctly unusual as presenting symptoms of MS. Imaging features that suggest ADEM rather than MS include white matter changes that extend from the subcortical region to the cerebral cortex, thalamic involvement, and demyelination that spans multiple contiguous spinal cord levels. Spinal fluid usually shows a mild-to-moderate lymphocytosis. Oligoclonal bands are less common in ADEM than in MS. Despite the apparent abundance of clinical and laboratory clues that help to distinguish between ADEM and MS, the two diagnoses may resemble each other at presentation, and the only definitive way to separate them is by observing the patient over time: the monophasic, non-relapsing course of ADEM distinguishes it from the relapsing or progressive course of MS. An attack of ADEM is usually treated with methylprednisolone (1 g IV × 5 d). Intravenous immunoglobulin and plasmapheresis are options for patients with severe disease or incomplete response to steroids.

Progressive Multifocal Leukoencephalopathy (PML)

PML is a life-threatening central nervous system demyelinating disorder caused by the JC polyomavirus in immunosuppressed patients. The most common responsible source of immunosuppression is HIV with CD4 counts <200 cells/mm^3. Immunosuppressive agents, especially natalizumab and other monoclonal antibodies, are the other important precipitants of PML. It may affect any area of the cerebral white matter but especially the frontal, parietal, and occipital lobes [23]. The clinical deficits correlate with the location of the pathology and typically include cognitive, motor, and visual field abnormalities. Encephalopathy and seizures may

occur. In some cases, the cerebellum is affected leading to an ataxic disorder. PML lesions differ from MS lesions in that they tend to be larger and often involve the gray-white junction. The diagnosis is established by finding positive JCV PCR in the CSF in the appropriate clinical context. In some cases, brain biopsy is required. There is no effective treatment for PML, though mefloquine and mirtazapine are often employed [24]. Optimizing highly active antiretroviral treatment is the best treatment option for PML associated with HIV, though survival is low even when this is accomplished [25]. Reducing or discontinuing relevant immunosuppressive medications including natalizumab is important, if applicable [26]. Plasma exchange to remove any responsible medication may be helpful. In small series, 1-year PML survival rates were 50–60% in patients with HIV and 75% in patients with PML related to natalizumab [27, 28].

Secondary Demyelinating Disorders: Reasonable Exclusion of Multiple Sclerosis Mimics

A wide variety of medical conditions may mimic MS, but surprisingly little guidance exists as to what constitutes a reasonable exclusion of alternative diagnoses. This is problematic, as some of the other causes of multifocal demyelination are at least partially reversible and do not lead to cumulative disability if treated properly. In a patient with a CIS, MRI findings highly suggestive of MS, and no other systemic signs of an alternate condition, additional diagnostic testing is seldom worthwhile. Tables 22.1, 22.2, 22.3, and 22.4 contain brief descriptions of the possible alternate diagnoses that must be considered when evaluating a patient with specific patterns of CNS demyelination.

Table 22.1 Differential diagnosis of isolated or combined cerebral, optic, and spinal presentations of MS

Disorder	Suggestive features	Evaluation
Systemic lupus erythematosus	Rash, kidney dysfunction	Anti-dsDNA and anti-Smith antibodies
Sjogren syndrome	Dry mouth, dry eyes	Sjogren antibodies
Neurosarcoidosis	Pulmonary symptoms	Biopsy showing noncaseating granulomas
Behcet disease	Oral and genital ulcers	Clinical diagnosis
Lyme disease	Rash, cardiac, and rheumatologic manifestations	Lyme antibodies, history or risk of tick exposure, bullseye rash
Mitochondrial encephalomyelopathy	Mental retardation, short stature, bilateral hearing loss	Elevated serum and CSF lactate, imaging abnormalities may involve the basal ganglia
Adrenoleukodystrophy	X-linked inheritance, adrenal dysfunction, peripheral neuropathy	Elevated very-long chain fatty acids
Metachromatic leukodystrophy	Autosomal recessive inheritance, prominent psychiatric dysfunction, peripheral neuropathy	Decreased leukocyte arylsulfatase A level

Table 22.2 Differential diagnosis of predominantly cerebral presentations of MS

Disorder	Suggestive features	Evaluation
CNS vasculitis	Development of multiple symptoms in short time frame	Brain biopsy
Central nervous system lymphoma	History of immunosuppression, steroid responsiveness	Brain biopsy, slit-lamp examination, and vitreous biopsy
Progressive multifocal leukoencephalopathy	History of immunosuppression	JC PCR in CSF
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)	Dementia, headache, multiple brain infarctions	NOTCH 3 mutation
CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids)	MRI demonstrating pontine perivascular enhancement	MRI is suggestive, confirmed by response to corticosteroids

Table 22.3 Differential diagnosis of predominantly spinal presentations of MS (see also Chap. 17)

Disorder	Suggestive features	Evaluation
Tropical spastic paraparesis	Patient from the Caribbean, Japan, or Africa	HTLV PCR testing
Spinal cord dural arteriovenous malformation	Waxing and waning symptoms	Spinal angiography
Cervical spondylosis	Neck pain, signs and symptoms of osteoarthritis elsewhere	Imaging of cervical spine
B_{12} deficiency	anemia, large-fiber polyneuropathy	Low B_{12}, elevated methylmalonic acid, elevated homocysteine
Copper-deficiency myelopathy	Progressive, painless myelopathy	Low serum copper levels
Hereditary spastic paraplegia	Inherited in mostly autosomal dominant fashion, may be associated with other neurologic signs and symptoms	Genetic testing available for more common mutations
Vitamin E deficiency	Prominent sensory ataxia and diarrhea	Low vitamin E levels
Spinocerebellar ataxia	Ataxia and dysarthria are prominent	Genetic testing available for more common mutations

Table 22.4 Differential diagnosis of optic neuropathy (see also Chap. 5)

Disorder	Suggestive features	Evaluation
Leber hereditary optic neuropathy	Subacute bilateral progressive visual loss	Genetic testing available for more common mutations
Nutritional optic neuropathies	Other signs of B_1 (beriberi) or B_{12} deficiency	Low B_1 or B_{12} levels
Retinal artery occlusion	Sudden-onset symptoms	Funduscopic examination
Toxic optic neuropathies	Exposure to toxins such as methanol, ethylene glycol, amiodarone, or ethambutol	History of relevant exposure

Treatment of Clinically Isolated Syndromes

Treatment of Optic Neuritis

Patients with optic neuritis are among the most heavily studied and carefully followed cohorts of patients with neurologic disease. Patients in the treatment arm of the Optic Neuritis Treatment Trial (ONTT) received methylprednisolone 250 mg IV qid × 3 days followed by oral prednisone 1 mg/kg/d PO for 11 days [29]. Because this regimen may be impractical in the hospital, a methylprednisolone dose of 1 g IV qd × 3 days is often employed with or without a prednisone taper in clinical practice. Sequential follow-up of patients in the ONTT offers several important pieces of information:

- Treatment with methylprednisolone hastens recovery but does not improve the typically excellent long-term visual prognosis of optic neuritis [29].
- Patients with optic neuritis who receive intravenous methylprednisolone have a decreased probability of developing MS in the short term (2 years) [30].
- Methylprednisolone does not reduce the lifetime chance that a patient with optic neuritis will develop MS [31].
- At 15 years, the overall probability that a patient with optic neuritis will develop MS is 50%. The long-term risk of developing MS may be stratified by brain MRI findings at the time of presentation [31]:
  - 25% for patients with 0 lesions
  - 60% for patients with 1 lesion
  - 68% for patients with 2 lesions
  - 78% for patients with 3 lesions

Treatment with disease-modifying therapy, therefore, should be considered strongly for patients with optic neuritis and one or more brain MRI lesions.

Treatment of Other Clinically Isolated Syndrome Suggestive of Multiple Sclerosis

The data to support treatment of CIS other than optic neuritis are less robust. Management decisions for patients with CIS depend on the severity of their deficits and likelihood of developing MS. Patients with mild deficits do not necessarily require any acute treatment. Use methylprednisolone for patients with more severe deficits, as it hastens symptom resolution. Although there is no dose which is clearly the most effective, methylprednisolone 1000 mg IV × 3 d is used most often.

Disease-Modifying Treatment for Patients with CIS

In addition to managing acute symptoms with corticosteroids, patients with CIS and MRI studies with lesions consistent with MS should be treated with a disease-modifying therapy to try to reduce the risk of relapses and delay the development of clinically definite MS [32].

Treatment of Relapsing-Remitting MS

Relapsing-remitting MS (RRMS) is the disease stage that usually follows CIS and is characterized by episodic flares separated by remissions. Almost all patients should be treated with immunomodulatory treatments. In general, if a disease-modifying therapy proves ineffective at 6 months, switching to a different agent should be considered [33].

Treatment of MS Flares

The three possible explanations for new symptoms in a patient with MS are new demyelinating lesions, pseudoexacerbation (unmasking of old deficits by superimposed infectious or metabolic insults), and unrelated neurologic disease. Screen all patients with new deficits for possible infectious and metabolic exacerbants by measuring complete blood count, electrolytes, glucose levels, urinalysis, and chest X-rays. Contrast-enhanced MRI is often necessary to distinguish active MS lesions from other causes of neurologic symptoms. In general, patients with MS flares should be treated with a 3-day course of 1000 mg intravenous methylprednisolone. Oral methylprednisolone (1000 mg qd × 3 days) and prednisone (1250 mg qd) are options for patients who prefer or require outpatient treatment [34, 35]. Plasmapheresis may be considered for patients with severe relapses or those which do not improve with steroid treatment [36].

Interferon-β

The exact mechanism of action of interferon-β in MS is unclear, though multiple studies show that it is an effective treatment option for relapsing-remitting MS [32]. The three available interferons are:

- IFN-β-1a (Avonex) 30 μg IM injection weekly
- IFN-β-1a (Rebif) 22 or 44 μg SC three times a week
- IFN-β-1b (Betaseron) 250 μg SC every other day

Common side effects of interferon therapy include flulike reactions, joint aches, injection site reactions, headaches, and depression. More serious side effects include lymphopenia, thrombocytopenia, thyroid dysfunction, asymptomatic transaminitis, and, rarely, hepatic failure. Patients should, therefore, undergo complete blood counts, liver function tests, and thyroid function tests upon initiation of interferon therapy and periodically thereafter. Studies suggest that high-dose interferon formulations may reduce the subsequent number of flares compared to lower-dose formulations [37, 38].

Glatiramer Acetate

This semirandom amino acid mixture reduces the number of relapses and possibly slows disease progression in patients with relapsing-remitting MS [39]. Glatiramer acetate is administered subcutaneously at a dose of 20 mg qd. Side effects include injection site reactions, chest pain, flushing, and tachycardia. Patients who take glatiramer acetate do not require any blood tests for monitoring purposes.

Natalizumab

Natalizumab is an α_4-integrin antagonist which is believed to work by preventing leukocyte migration across the blood-brain barrier, thereby reducing CNS inflammation. It decreases the number of flares, reduces radiologic evidence of active disease, and slows disease progression [40]. Natalizumab is prescribed exclusively as monotherapy, at a dose of 300 mg IV every 4 weeks. It is used for patients with poorly controlled MS, and not as a first-choice agent for most patients because it is associated with an estimated 1 in 500 risk of developing progressive multifocal leukoencephalopathy (PML) [41]. The three factors that increase the risk for developing PML are elevated serum JC virus antibody index, greater duration of natalizumab use, and prior immunosuppressant use [42]. Because PML is difficult to treat and often fatal, its potential to develop must be discussed seriously with any natalizumab candidate [43]. After starting treatment, JCV antibodies should be checked again at 6 months and at a year. Consider stopping the medication if the JCV antibody status becomes positive upon repeat testing. Other risks of natalizumab include an increased incidence of melanoma and liver injury. Because of the potential hazards, many patients who receive natalizumab do so for only short stretches of 2 years as a form of induction therapy, before switching to a different therapy.

Fingolimod

Fingolimod is an orally administered (0.5 mg qd) sphingosine-1-phosphate analog that works by sequestering autoreactive T cells in lymph nodes [44, 45]. It is prescribed most often for patients who have had relapses with interferon or glatiramer

acetate and who have JCV antibodies, excluding them from natalizumab treatment. Fingolimod may cause bradycardia, and the first fingolimod dose requires extended EKG monitoring for 6 hours to make sure that the patient does not develop bradycardia. Medications that prolong the QT interval should be avoided. Macular edema manifested clinically by blurred vision, visual distortions, and scotomata is another possible side effect. Fingolimod candidates should undergo ocular computed tomography before medication initiation and 3–4 months later. Reactivation of viral infections including HSV and VZV is another potentially important side effect of fingolimod treatment. Patients taking fingolimod need to undergo monitoring of white blood cell counts and liver function tests every 3 months after initiation. PML develops rarely in patients who have received fingolimod.

Dimethyl Fumarate

Dimethyl fumarate is an oral medication that reduces the rate of relapses and possibly disease progression in patients with relapsing-remitting multiple sclerosis [46, 47]. It is started at a dose of 120 mg bid and increased to 240 mg bid after a week. Dimethyl fumarate is used most often for patients who prefer an oral medication, who are not candidates or do not want to receive natalizumab infusions, and who failed treatment with interferon or glatiramer acetate. The most common side effect of dimethyl fumarate is facial flushing, which can be severe enough to require that the medication be discontinued. Gastrointestinal irritation with diarrhea and abdominal pain may also occur. Periodic testing for lymphopenia and liver dysfunction should occur. Consider stopping dimethyl fumarate for patients with persistent lymphopenia, as this increases the risk for developing progressive multifocal leukoencephalopathy [48].

Teriflunomide

The oral antimetabolite teriflunomide, administered at a dose of 7–14 mg qd, reduces MS relapses and the risk of progression [49, 50]. Potential side effects include hair loss and gastrointestinal distress. Periodic complete blood count and liver function tests should occur to screen for lymphopenia and hepatotoxicity. Because it is highly teratogenic, women of childbearing age must have a negative pregnancy test prior to beginning the medication, should be counseled on the potential side effects to a fetus, and should use contraception while taking it.

Alemtuzumab

Alemtuzumab is a monoclonal antibody which binds CD52, resulting in lymphocyte depletion. It is administered intravenously, 12 mg per day × 5 infusions followed 12 months later by 12 mg per day × 3 days. It reduces relapses in patients

with MS, but, due to side effects, is only administered after a patient has failed other therapies [51, 52]. Side effects of alemtuzumab include infusion reactions, infections, autoimmune diseases, and increased malignancy risk.

Ocrelizumab

Ocrelizumab is a CD20 monoclonal antibody that is used for relapsing-remitting and for progressive forms of MS [53, 54]. It is an intravenous medication administered as two doses of 300 mg separated by 2 weeks followed by a dose of 600 mg every 6 months. Infusion reactions are common with ocrelizumab, but are usually mild and tolerable. Hepatitis serologies must be checked prior to starting ocrelizumab, as it may cause reactivation of a latent hepatitis B infection.

Choosing a First Disease-Modifying Therapy

There is no disease-modifying therapy that can be recommended universally to treat a patient with newly diagnosed MS. A balance must be struck between medication efficacy and toxicity, and health insurers may deny more potent or most costly medications unless there is evidence of failure with one of their preferred medications. In general, patients with newly diagnosed MS can be divided into two groups:

- The first group has mild and non-disabling symptoms without a severe burden of radiologic disease. For these patients, I will use an interferon, glatiramer acetate, teriflunomide, or dimethyl fumarate.
- The second group of MS patients has more severe, often-disabling symptoms and a higher burden of radiologic disease. For these patients, I will recommend treatment with natalizumab. Some patients with severe disease are reluctant to consider natalizumab because of the risk for PML. It is important to discuss risk stratification with these patients and counsel them that it may be in their best interest to start natalizumab early in the course of MS before they have received other immunosuppressants in order to reduce long-term disease burden and the risk of developing PML. For patients with more severe disease who are not appropriate candidates for natalizumab or who are unwilling to risk taking the medication, other appropriate treatment options are dimethyl fumarate, fingolimod, and ocrelizumab, though these agents also have either theoretical or actual risks of causing PML.

Switching Disease-Modifying Therapy

The decision to switch between disease-modifying therapies is challenging. It is important to use clinical judgment when making a medication switch rather than adhering to a set of ironclad rules, because there is considerable uncertainty surrounding the critical questions:

- Does one relapse constitute evidence of inefficacy?
- Should silent lesions appearing on a serial screening MRI indicate treatment failure?
- Should switching occur within a tier of medications, or is it necessary to escalate to the next tier of medications?

In general, I will wait at least 6 months after starting a disease-modifying therapy before declaring a clinical relapse evidence of treatment failure. For patients who have milder clinical and radiologic disease and who are tolerating their first treatment, it may be appropriate to wait for a second relapse to consider a new medication. The risks of switching to a more potent but likely more toxic agent such as natalizumab, ocrelizumab, or alemtuzumab must be considered when making any switch.

Poor patient tolerance of side effects may prompt a switch between disease-modifying therapies:

- For patients who are taking glatiramer acetate or interferons and are having difficulty with injections but are otherwise doing well, consider switching to an oral medication such as dimethyl fumarate, or teriflunomide may be appropriate.
- For patients who develop progressive multifocal leukoencephalopathy or seroconvert to JCV Ab-positive status while taking natalizumab, consider switching to fingolimod after a washout period of between 6 and 12 weeks [55, 56].

Progressive MS and Symptomatic Treatment

Unfortunately, approximately 80% of patients with MS have progressive disease. Distinct flares are less frequent in this stage, but disability due to both brain and spine disease may lead to loss of ambulation, inability to perform activities of daily living, and eventually nursing home placement and death. Progressive deterioration from disease onset is known as primary progressive MS (PPMS) which occurs in approximately 10% of patients with MS and is more likely in older than younger ones [57]. Deterioration that develops after several relapses and remissions is known as secondary progressive MS (SPMS) and may develop after many years of disease stability or after just a few relapses. The median time to develop SPMS after MS diagnosis is approximately 20 years, with male gender and the presence of motor symptoms being predictive of shorter times to SPMS onset [58].

Disease-Modifying Therapy

Disease-modifying therapies are not as effective for progressive MS as they are for relapsing-remitting MS. In many cases it is appropriate to discontinue disease-modifying therapies altogether. Ocrelizumab may slow progression in patients with primary progressive MS and is approved for this indication [54]. Other treatment options that have been employed with varying success for patients with progressive

disease include monthly steroid infusions, methotrexate, azathioprine, plasmapheresis, intravenous immunoglobulin, and stem cell transplantation.

Symptomatic Treatment

Spasticity

Spasticity secondary to MS may lead to intense pain and impaired mobility. Physical therapy emphasizing range of motion exercises is only modestly helpful, but, in some cases, may prevent contractures. Baclofen (initiated at 10 mg tid and titrated upwards to a maximum daily dose of 80 mg) is usually the first line of treatment for spasticity secondary to MS. In patients who do not respond to baclofen, alternative treatment options include tizanidine (2–8 mg tid), dantrolene (25–100 mg tid), and diazepam (5–20 mg tid). Consider referring patients with refractory symptoms for intrathecal baclofen pump placement. Although botulinum toxin injections are theoretically helpful, most MS patients require injections in many muscles, which may be impractical.

Urinary Dysfunction

The majority of patients with progressive MS will develop some degree of bladder dysfunction [59]. After excluding urinary tract infection by performing urinalysis and treating any relevant infection, the next step in evaluating bladder complaints is to try to localize the problem:

- Cervical and upper thoracic level lesions produce a spastic bladder and urge incontinence. The patient has a sudden urge to urinate and cannot make it to the bathroom in time.
- Mid-to-lower thoracic level lesions result in detrusor sphincter dyssynergia in which the urinary detrusor contracts against a closed urethral sphincter. The patient has difficulty voiding and feels as if they are straining excessively in order to produce even a weak urinary stream.
- Lumbosacral level lesions lead to bladder hypotonia and overflow incontinence. The patient feels that they are emptying their bladder incompletely and notes intermittent urinary leakage.

Because patients often describe their urinary symptoms inaccurately, measuring a post-void urine residual volume may be necessary to localize the problem. Incontinence in a patient with a post-void residual of less than 100 cm^3 is most likely due to a spastic bladder with urge incontinence and should be treated with an anticholinergic agent such as oxybutynin (5 mg bid-qid) or tolterodine (1 mg qd–2 mg bid). Incontinence in a patient with a post-void residual of greater than 100 cm^3 is most likely due to a flaccid bladder with overflow incontinence and

should be treated with intermittent straight catheterization. Patients who do not respond to anticholinergic agents or intermittent straight catheterization should be referred for formal urologic evaluation. Refractory symptoms may require an indwelling suprapubic catheter, botulinum toxin injections, or sacral stimulator placement.

Fatigue

Fatigue is often the most prominent and disabling chronic MS symptom. It is not due to a specific lesion but may be a marker of disease progression. Patients with MS describe exhaustion, myalgias, and impaired concentration, though they usually do not report a specific urge to sleep. Screen for contributors to fatigue including medications, depression, stress, and environmental changes such as heat. Lifestyle modifications including education about the sources of fatigue, sleep hygiene, and exercise programs are often the most effective interventions. Medications that may be variably effective include amantadine, aspirin, selective serotonin reuptake inhibitors, and stimulants. While modafinil (200 mg qam) helps many patients with daytime sleepiness, it may do little for patients with fatigue related to MS.

Depression and Anxiety

Depression and anxiety affect approximately 50% of patients with MS [60]. These symptoms are secondary to a combination of the neurodegenerative process and psychological maladjustment to the disease. Patients with MS and depression or anxiety usually benefit from a combination of cognitive-behavioral therapy and SSRIs. Short-acting anxiolytics should be used cautiously for patients with anxiety. Social workers, psychiatrists, and psychologists play an important role in addressing adjustment problems.

Cognitive Dysfunction

Cognitive dysfunction develops in about half of patients with MS and is usually a manifestation of the later stages of the disease [61]. The classic pattern of cognitive impairment in MS is “subcortical dementia” in which processing speed and attentional problems outweigh cortical defects such as aphasia and apraxia. Whether disease-modifying agents reduce the probability or slow the onset of dementia is unclear. Patients with dementia secondary to MS are treated in much the same fashion as those with other forms of dementia (Chap. 4). Donepezil is used most frequently, though it has not necessarily shown efficacy in MS patients [62].

Pain and Paresthesias

Sensory symptoms affect almost all patients with MS. Agents such as gabapentin, nortriptyline, and pregabalin are employed in much the same fashion as for other patients with neuropathic pain (Chap. 15). Trigeminal neuralgia is particularly common in patients with MS. Conventional treatments for this condition include

carbamazepine, phenytoin, and gabapentin (Chap. 19). The prostaglandin E1 analog misoprostol (600 μg qd) is an additional treatment option specifically for trigeminal neuralgia for MS patients [63]. Stereotactic radiosurgery may be useful for patients with refractory symptoms [64].

Motor Impairments

Motor decline is usually the symptom which is of greatest concern to patients with newly diagnosed MS. The course of each individual MS patient is different and somewhat difficult to predict, but the median time to require a walking aid is between 15 and 30 years [57, 65]. These data, however, were obtained on patients who did not have access to effective immunomodulatory therapies for MS, and it is likely that the long-term motor prognosis will improve now that such therapies are more readily available. Physical therapy and physiatry consultations are helpful to teach effective compensatory strategies and to determine the need for assistive devices. Dalfampridine (4-aminopyridine) 10 mg bid may help gait dysfunction in MS [66].

Tonic Spasms

Tonic spasms are brief (usually seconds in duration) episodes of painful, tetanic spasms involving one side of the body that are often precipitated by movement or hyperventilation [67]. They are likely produced by ephaptic transmission within the spinal cord. Fortunately, they are short-lived and usually respond to treatment with carbamazepine.

Fulminant MS

Rare, fulminant variants of MS cause rapidly progressive disability and sometimes death. The two best-known examples are Balo concentric sclerosis and Marburg variant MS. Balo concentric sclerosis is pathologically and radiologically characterized by rings of demyelination alternating with rings of preserved myelin (Fig. 22.5). In Marburg variant MS, there is progression of deficits to severe disability or death within a few weeks to months [68]. Immunomodulatory therapy must be initiated quickly and aggressively for patients with rapidly progressive MS variants. Most patients should undergo plasmapheresis in addition to corticosteroid treatment. Other chemotherapeutic agents including cyclophosphamide may be helpful if prescribed at an early enough stage of fulminant MS, though there is little high-level literature to support any particular treatment.

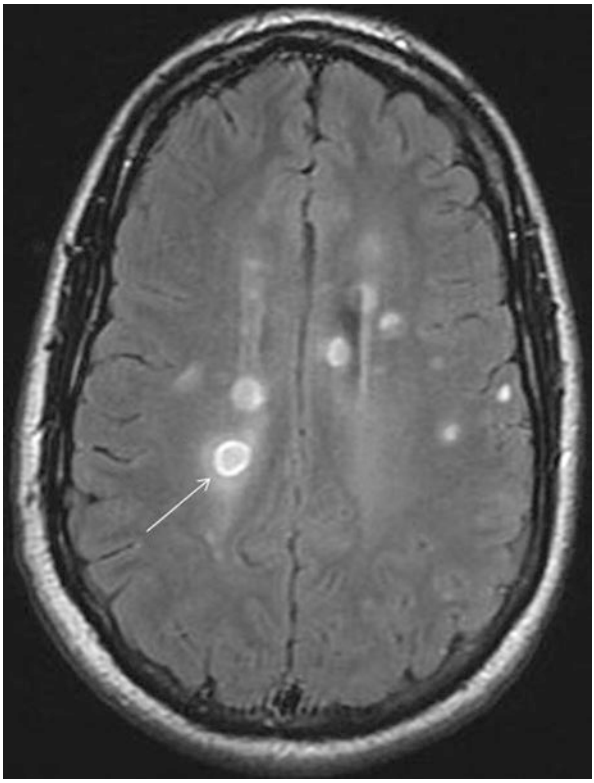

Fig. 22.5 Axial FLAIR MRI showing Balo concentric sclerosis, a severe variant of MS characterized by alternating concentric rings of demyelination and remyelination

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Intracranial Mass Lesions

23

Introduction

Intracranial mass lesions may come to clinical attention by producing headaches, seizures, or other focal neurological findings. Some mass lesions are life-threatening, placing the patient at risk for increased intracranial pressure. Others are found incidentally on a neuroimaging study ordered for another reason. The important imaging features of a mass lesion are its location and appearance (size, shape, and infiltrating vs. space-occupying appearance). This chapter reviews common intracranial mass lesions in adults. Many pediatric tumors or less common masses are not discussed, and the reader is instead referred to a more comprehensive neuro-oncology text [1].

Supratentorial Masses

Metastatic Tumors

Metastatic tumors are the most common space-occupying supratentorial tumors in adults. Their diagnosis is usually straightforward in patients with a known primary tumor but more challenging when a metastatic lesion is the first presentation of cancer. Four radiologic features help to differentiate metastatic lesions from other intracranial masses: they tend to be multiple, they are located at the gray-white junction, they are well circumscribed, and they are associated with variable amounts of surrounding vasogenic edema (Fig. 23.1) [2].

The first step in evaluating and treating a patient with suspected cerebral metastasis is to address the associated mass effect and surrounding edema. In some patients the mass effect and edema are minor and do not require any aggressive treatment. In others, vasogenic edema leads to increased intracranial pressure and can be life-threatening. Treat patients with symptomatic vasogenic edema with a 10–20 mg loading dose of dexamethasone followed by 4 mg qid. When prescribing

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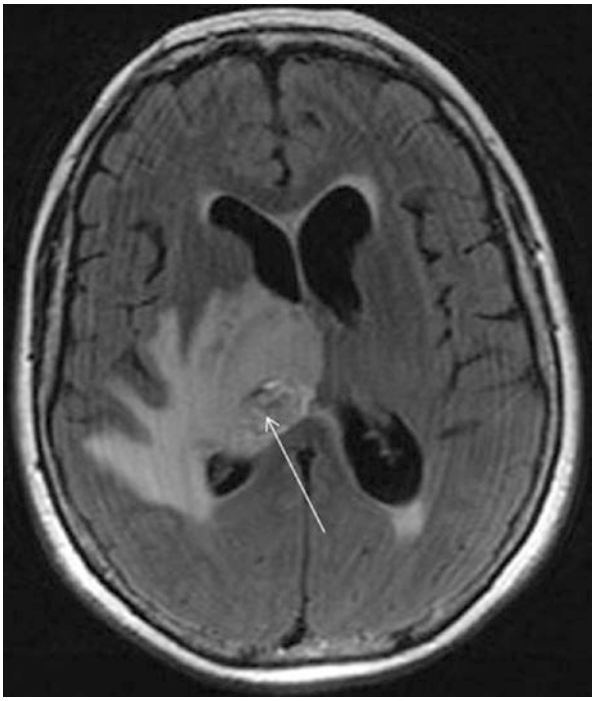

Fig. 23.1 Axial FLAIR MRI shows metastasis (arrow) with large amount of surrounding cerebral edema

dexamethasone be sure to provide gastrointestinal ulcer prophylaxis with an H2 blocker or proton pump inhibitor. Corticosteroids may not reduce edema for several days, and in some cases, more aggressive measures to address elevated intracranial pressure may be necessary (Chap. 2). Once vasogenic edema is under control, dexamethasone may be tapered slowly over several weeks.

The next step in managing a patient with cerebral metastasis is to define the origin of the tumor. In some patients, the cancer diagnosis is already known, but it should not be assumed that this cancer is the source of metastasis, especially in patients with cancers that are unlikely to spread to the brain. Tumors with a propensity to metastasize to the brain include carcinomas of the lung, breast, and kidney, and melanoma. Although less likely to spread to the brain, gastrointestinal tract cancers are important sources of metastasis because of their prevalence. Lung cancer accounts for the majority of tumors (up to 80%) in patients with brain metastasis and a yet unidentified primary brain tumor [3]. Evaluation for an unknown primary tumor should start with a CT scan of the torso with and without contrast and careful dermatologic assessment. Women should undergo mammography. Although tumors of the prostate and testicular region are less frequent sources of metastases, men require directed testicular examination, scrotal ultrasound, and prostate-specific antigen measurement if no other primary source is found. In some patients, a thorough medical evaluation does not disclose the source of the metastasis, and the primary tumor is defined only after brain biopsy.

Definitive management of metastatic cerebral disease depends on the number and location of the metastases, patient age, and the status of the primary cancer.

Patients with a small number (three or fewer) of surgically accessible lesions and otherwise favorable prognoses are candidates for tumor resection followed by stereotactic radiosurgery [4]. Those with inaccessible lesions but otherwise good prognoses should undergo stereotactic radiosurgery. Patients with multiple, surgically inaccessible lesions and otherwise poor prognoses due to systemic disease should receive palliative whole brain radiotherapy. Targeted chemotherapy may be an option for patients with specific lung cancers, breast cancers, and melanoma. The life expectancy of patients with cerebral metastases ranges from a few months to 1–2 years. As might be expected, younger patients, those with better overall health and function, and those with fewer metastases have better prognoses [5].

Gliomas

Gliomas are the most common primary malignant intracranial neoplasms. Most glial tumors that come to clinical attention are high-grade tumors including glioblastomas, anaplastic astrocytomas, and anaplastic oligodendrogliomas. Among these, glioblastomas are the most common. They tend to affect patients in their 50s through 70s. Common presentations include headaches and seizures. High-grade gliomas are typically hypodense on T1-weighted images and enhance heterogeneously (Fig. 23.2). They may have space-occupying or infiltrating characteristics. The diagnosis must be made by examining tissue, preferably by gross total lesion resection, but via stereotactic biopsy should the lesion prove to be too large or

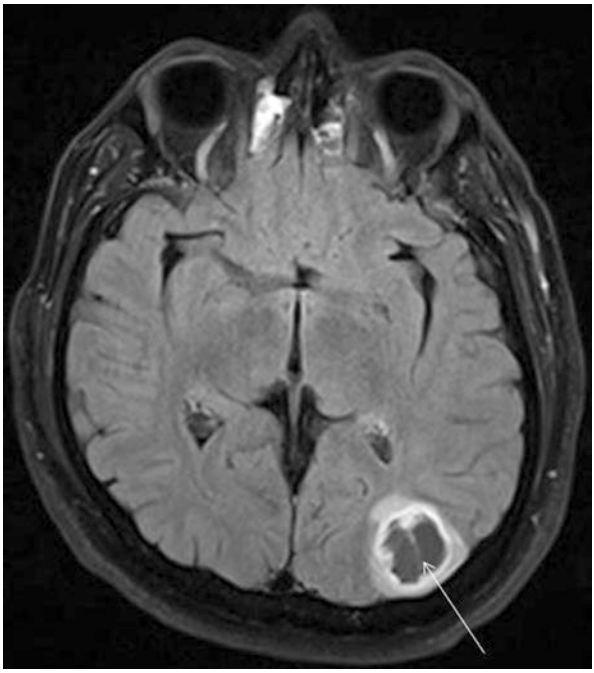

Fig. 23.2 Contrast-enhanced T1-weighted MRI of a high-grade glial tumor shows a hypodense occipital lesion with a ring of surrounding enhancement and scant edema

surgically inaccessible. Once tissue is obtained and a diagnosis of a high-grade glioma is established, molecular markers are analyzed to assist with treatment and prognosis:

- Loss of heterozygosity on chromosomes 1p and 19q (1p/19q codeletion) is associated with better prognosis and response to the combination of radiation and chemotherapy [6].
- Isocitrate dehydrogenase (IDH) mutations are associated with better prognosis [7].
- Methyl guanine methyl transferase (MGMT) promoter methylation is associated with improved response to temozolomide and better prognosis [8].

Unfortunately, glioblastomas have a poor prognosis, with survival averaging 14–16 months. Older patients with poorer functional statuses tend to do worse. Patients who choose aggressive therapy should be treated with a combination of maximal resection followed by adjuvant radiation therapy and the oral alkylating chemotherapeutic agent temozolomide [9]. Temozolomide is particularly useful for patients who have glioblastoma associated with methylation of the MGMT promoter [8]. The VEGF monoclonal antibody bevacizumab may improve progression-free survival and quality-of-life measures but does not improve overall survival in glioblastoma patients [10, 11].

Low-grade gliomas (including astrocytomas and oligodendrogliomas) tend to affect patients in their 20s through 40s. They tend to be based in the white matter but may infiltrate the cerebral cortex. Most low-grade gliomas do not enhance with contrast. Seizures are more common in patients with low-grade gliomas than in patients with glioblastoma or other higher-grade gliomas (Chap. 20). Patients with low-grade gliomas should undergo surgical resection if surgery is technically feasible [12]. Selection of postoperative adjuvant radio- and chemotherapy is based on histologic tumor grade and molecular diagnostic test results; a full discussion is beyond the scope of this text [13].

Deterioration in Patients with Gliomas

Deterioration in patients with gliomas may be due to stroke, infection, seizures, and adverse medication effects. The most important sources of deterioration are tumor recurrence and progression, radiation-induced pseudoprogression, and radiation necrosis. Each may produce vague symptoms including headache, fatigue, and encephalopathy or may lead to findings identical to the presenting tumor symptoms. These conditions are often difficult to distinguish from each other radiologically: magnetic resonance spectroscopy (MRS), FDG-PET, and perfusion studies may be helpful, but in many instances, brain biopsy is required for diagnosis.

Glioma Recurrence and Progression

Eventually, high-grade gliomas will recur and progress. Patients with glioma recurrence may benefit from resection, additional radiotherapy, or bevacizumab [14].

Radiation-Induced Pseudoprogression

Radiation-induced pseudoprogression is the re-expression of initial tumor deficits up to 3 months after radiation treatment [15]. It is typically a radiologic finding due to increased vascular permeability and produces no or minimal deficits. For most patients with radiation-induced pseudoprogression, watchful waiting with anticipation of resolution is appropriate, but some patients may require corticosteroids.

Radiation Necrosis

Radiation necrosis is a problem that occurs months to years after radiation for brain tumors and is usually seen in patients who have received higher radiation doses (more than 72 Gy total) [16]. Radiation necrosis can be treated in a variety of ways, depending on the severity of the lesion. Observation may be acceptable for minimally symptomatic patients. Corticosteroids are usually employed if neurologic deficits are present. Bevacizumab and hyperbaric oxygen are options for patients with refractory disease [17]. Surgical debulking is rarely indicated but may be needed for patients with severe, medically unresponsive radiation necrosis.

Meningiomas

Meningiomas are the most common benign intracranial tumors. They are often asymptomatic, but some come to clinical attention by producing headaches, seizures, or focal neurologic abnormalities. Common sites are the cerebral convexities, skull base, and sellar region. Radiologically, meningiomas are smooth-appearing, durally based, space-occupying masses that enhance homogeneously with contrast (Fig. 23.3). Calcification is common. The radiologic differential diagnosis of meningiomas includes dural metastasis and benign dural calcification. Most incidental meningiomas may be followed with yearly clinical examination and MRI to assess stability [18]. Surgically accessible, symptomatic meningiomas and those which show evidence of expansion should be resected. Radiation may be considered for patients with higher-grade tumors and when surgical resection is incomplete [19].

Primary Central Nervous System Lymphomas (PCNSL)

PCNSL are most commonly diffuse large B-cell-type non-Hodgkin lymphomas isolated to the central nervous system. They may occur in both immunocompetent and immunosuppressed patients. PCNSL usually presents with headaches, behavioral changes, or focal neurologic findings. They are most commonly solitary, periventricular lesions that enhance with contrast. A classic but uncommon radiographic finding is crossing of the corpus callosum. Lymphomas are extremely sensitive to steroids, and because steroids may obscure the diagnosis, they should not be administered until PCNSL is confirmed histologically. In practice, delaying steroid administration is not always feasible, as many patients present with problems related to increased intracranial pressure or rapid deterioration that requires steroid treatment before a firm

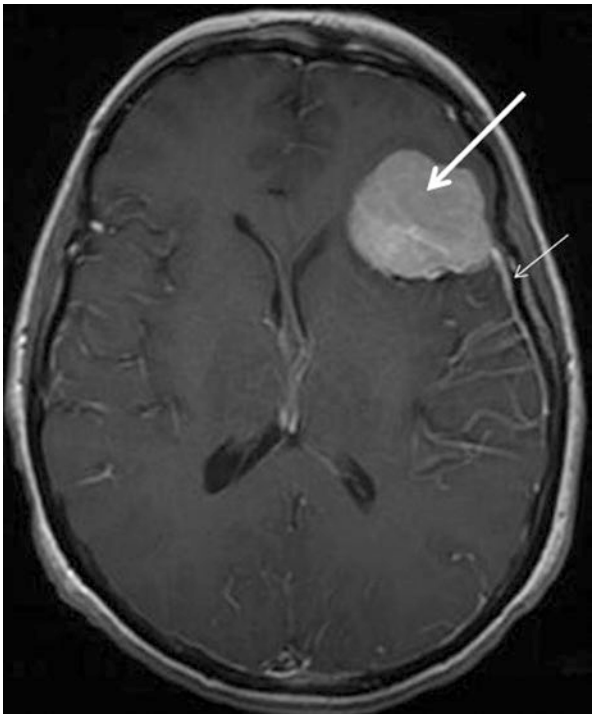

Fig. 23.3 Contrast-enhanced T1-weighted MRI of a meningioma shows a homogeneously enhancing mass (thick arrow). Note the dural tail (thin arrow), a helpful sign in diagnosing meningioma

diagnosis can be established. Ophthalmologic evaluation including slit-lamp examination and vitreous biopsy should be considered as part of the evaluation. CSF analysis with flow cytometry may help to diagnose PCNSL. Ultimately, brain biopsy is required to establish the diagnosis in most cases. The mainstay of PCNSL treatment is methotrexate, usually in combination with other chemotherapeutic agents [20]. Although adding radiation therapy to methotrexate may improve survival, the combination of these two modalities is toxic and should be used with caution, especially in older patients. Younger patients with PCNSL with good performance status have median survivals of approximately 5 years, while older patients with poor performance status have median survival of approximately 1 year [21].

Arteriovenous Malformations

Arteriovenous malformations present in a variety of ways including hemorrhages, seizures, headaches, and focal neurologic signs such as hemiparesis or visual field cuts. They often present for the first time in childhood or young adulthood. The annual risk of hemorrhage from AVM is approximately 2–3%, and 20% of these hemorrhages will be fatal [22]. Beyond imaging studies, little is generally needed to make a diagnosis of an AVM: the vascular flow voids which resemble a bag of worms on MRI are pathognomonic (Fig. 23.4). Decisions concerning management of AVMs depend on their size, location, and presence of deep venous drainage (Table 23.1). In general, lesions with a Spetzler-Martin grade of I, II, or III should

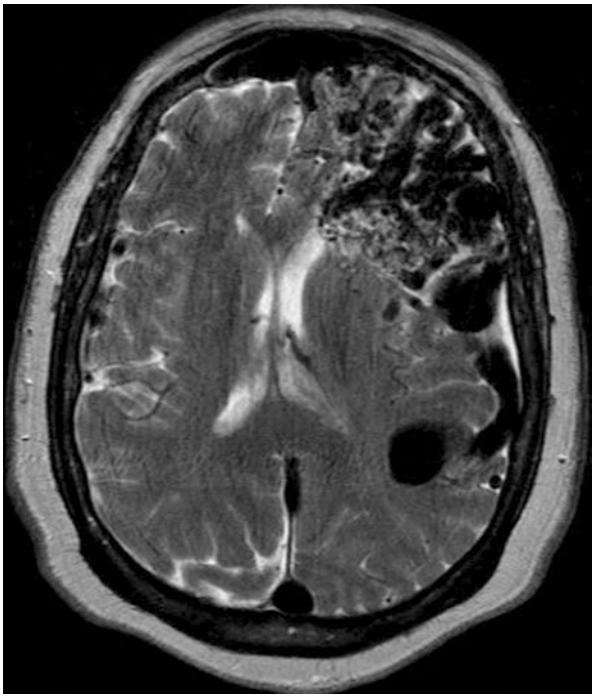

Fig. 23.4 T2-weighted axial MRI shows large frontoparietal arteriovenous malformation. The flow voids seen on T2 resemble a "bag of worms"

Table 23.1 Spetzler-Martin AVM Grading Scale

Size		
	0–3.0 cm	1
	3.1–6.0 cm	2
	>6.0 cm	3
Location		
	Noneloquent	0
	Eloquent	1
Deep venous drainage		
	Absent	0
	Present	1

The Spetzler-Martin grade is obtained by adding the numbers in the third column

be treated with a microvascular, endovascular, or radiosurgical approach [22, 23]. Grade IV and V AVMs are associated with high procedural morbidities, and decisions concerning interventions should be made very carefully based on the experience and comfort level of the treating neurosurgeon.

Abscesses

Intracranial abscesses are life-threatening infections that are usually acquired via direct spread (e.g., head trauma, neurosurgery, sinus infection, or dental infection) or as a result of hematogenous dissemination of an infection elsewhere. Headache is the most common symptom of abscess. Fever is another classical symptom but is present

inconsistently, and its absence leads to misdiagnosis. In more severe cases, abscesses may produce seizures or encephalopathy. The preferred neuroimaging study for evaluating an abscess is MRI with contrast, which characteristically shows a ring-enhancing lesion. The most common sites of abscesses are the frontal and temporal lobes. Multiple abscesses are common. Elevations of peripheral white blood cell count, ESR, and CRP may suggest the diagnosis. Lumbar puncture is not recommended as it is often non-diagnostic and may lead to cerebral herniation. While blood cultures may be positive in cerebral abscesses, definitive diagnosis is established via brain biopsy, aspiration, or excision. Common causes of abscesses in immunocompetent patients include gram-positive cocci, gram-negative rods, and anaerobic bacteria. Empiric therapy should include, therefore, a combination of vancomycin, ceftriaxone or cefotaxime, and metronidazole. Antibiotics may be tailored once a specific organism is identified. Aspiration or surgical excision may be required for patients with progressive mass effect or posterior fossa abscesses. Infectious disease consultation should be sought for assistance with diagnosis and treatment regimens.

Tumefactive Multiple Sclerosis

Multiple sclerosis (MS) may produce demyelinating lesions which resemble gliomas both clinically and radiographically. This so-called tumefactive MS leads to symptoms that are otherwise unusual in MS including seizures and headaches. Although there are no radiologic features that reliably distinguish between glioma and tumefactive MS, findings that are more consistent with MS include young age of onset, the presence of multiple lesions, and minimal perilesional edema [24]. Magnetic resonance spectroscopy may help to differentiate between tumefactive MS and glioma [25]. Brain biopsy, however, is the only definitive way to make the diagnosis.

Sellar Region Masses

Masses in the sellar region are often noted as incidental findings in patients with nonspecific headaches. In other patients, sellar masses are first detected when ocular motor abnormalities, visual field cuts, or hypothalamic-pituitary dysfunction develop. Approximately 90% of pituitary masses in adults are adenomas [26]. Less common masses include craniopharyngiomas, meningiomas, metastases, abscesses, and cysts. It is often difficult to distinguish among these masses radiographically. The first step in clinical decision-making for a sellar mass is to classify it by size, prolactin level, secretion of other hormones, and whether the mass is causing any neuro-ophthalmologic abnormalities [27]:

- Masses that produce progressive neuro-ophthalmologic abnormalities should undergo excision.
- Masses that secrete prolactin are prolactinomas and should be treated initially with dopamine agonists unless they cause neuro-ophthalmologic abnormalities.

- Masses that secrete hormones other than prolactin are functional adenomas and should undergo excision.
- Non-secretory masses that are smaller than 10 mm and that do not produce neuro-ophthalmologic abnormalities should be re-evaluated with MRI at 1 year. If there is no growth at that time, imaging studies should be repeated only if neuro-ophthalmologic or endocrine symptoms develop.
- Non-secretory masses larger than 10 mm that do not produce neuro-ophthalmologic abnormalities should be evaluated with MRI at 6 months and then yearly if no growth is observed.

Assistance of an endocrinologist and neurosurgeon should be obtained in all but the most straightforward cases.

Craniopharyngiomas are benign tumors that are derived from Rathke's pouch. Although they are more common in children, they may come to attention in older adults. The appropriate treatment is maximal surgical resection, with radiation being employed if there is residual tumor. Prognosis is usually good when local growth can be controlled.

Cerebellopontine Angle (CPA) Masses

The most common presentation of a CPA mass is hearing loss due to compression of the vestibulocochlear nerve. Because most CPA lesions grow slowly, compression of the vestibular portion of this nerve does not usually produce frank vertigo, but patients may feel off balance. Other structures in the CPA that may be compressed include the trigeminal nerve, facial nerve, cerebellum, and brainstem. Audiometry is important in the evaluation of suspected CPA masses to assess for hearing loss, even if the lesion has already been visualized radiographically.

Vestibular schwannomas (acoustic neuromas) account for most CPA tumors. These are usually unilateral, with the classic exception of neurofibromatosis type 2, in which schwannomas are present bilaterally. Decisions concerning vestibular schwannoma treatment depend on the size of the tumor and the symptom burden that it produces. Surgical resection is the best approach for younger patients with large, growing, or symptomatic tumors. Stereotactic radiosurgery may be appropriate for older patients and patients with smaller tumors. Because vestibular schwannomas grow slowly and are not malignant, patients with smaller, asymptomatic tumors may be followed with serial MRI scans every 6–12 months and more frequently if symptoms progress. Patients with faster growing tumors should be evaluated for surgical intervention. Despite a high success rate, surgical resection often produces hearing loss and facial nerve dysfunction and sometimes findings related to the brainstem and cerebellum. Targeted radiation therapy is also an option that may be equally effective as surgery and associated with fewer side effects.

Meningiomas represent a small but important minority of CPA masses. Uncommon CPA masses include cholesteatomas, gliomas, and metastases [28].

Masses in Immunocompromised Patients

AIDS patients, bone marrow transplant recipients, and other immunocompromised patients are susceptible to intracranial mass lesions which do not affect immunocompetent people. The two most important of these lesions are toxoplasmosis and PCNSL. Fungal abscesses are also relatively specific to immunocompromised patients. When evaluating an immunosuppressed patient with an intracranial mass lesion, it is important to not neglect the possibility of masses that also affect immunocompetent patients including primary and metastatic tumors.

Toxoplasmosis and Primary Central Nervous System Lymphoma

Toxoplasmosis (caused by reactivation of infection with the protozoan parasite *Toxoplasma gondii*) and primary central nervous system lymphoma (PCNSL) are the two intracranial masses which should be considered first in immunosuppressed patients. Both lesions occur in patients with CD4 counts lower than 200 cells/μL. Symptoms of toxoplasmosis include fevers, headaches, seizures, and focal neurologic findings. PCNSL is discussed above. Radiographic features may help to differentiate between the two but are not entirely reliable: toxoplasma lesions are more likely to be multiple and to have a ring-enhancing pattern (Fig. 23.5), while PCNSL is more likely to be a solitary mass and to involve or cross the corpus callosum. The usual protocols to differentiate between toxoplasmosis and PCNSL are:

- In neurologically stable patients: treat for toxoplasmosis empirically with pyrimethamine loading dose 200 mg followed by 50–75 mg qd and sulfadiazine 1000–1500 mg qid.
- If the lesions decrease in size on subsequent MRI, the diagnosis is toxoplasmosis, and appropriate treatment should be continued with the guidance of an infectious disease specialist. If the lesions do not decrease in size, then arrange for brain biopsy.
- In patients with severe neurologic deficits, including impending herniation, initiate dexamethasone (10 mg × 1 followed by 4 mg qid) and arrange for diagnostic brain biopsy and resection of the mass.

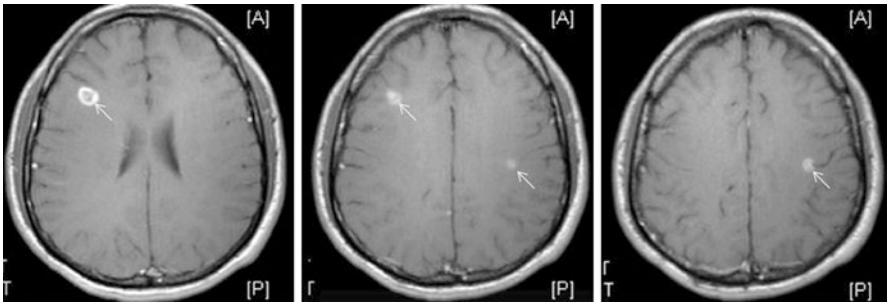

Fig. 23.5 Multiple contrast-enhancing T1 lesions, some of which are ring-enhancing, in a patient with HIV and a CD4 count of 90 cells/μL, consistent with toxoplasmosis

Fungal Abscesses

The most important fungi that form abscesses specifically in immunocompromised patients are *Aspergillus*, *Candida albicans*, *Coccidioides immitis*, and *Cryptococcus neoformans*. Evaluation of suspected abscess should include fungal blood cultures and spinal fluid analysis, provided that the abscess is not producing substantial mass effect. Treatment should be supervised by an infectious disease specialist. Unfortunately, outcome of fungal abscesses in immunocompromised patients is poor.

Masses in Patients from the Tropics and Developing World

Neurocysticercosis

Infection with the pork tapeworm *Taenia solium*, leading to neurocysticercosis, is common in patients from Latin America, Africa, and Asia. The important life cycle stages are the active cyst stage, which classically produces seizures (Chap. 20), and the calcified cyst stage, which is usually asymptomatic and noted during a neuroimaging study for another indication (Fig. 23.6). Neurocysticercosis may also lead to ventricular obstruction and increased intracranial pressure. Both MRI and CT are used to diagnose neurocysticercosis. Active lesions enhance on MRI, and in some

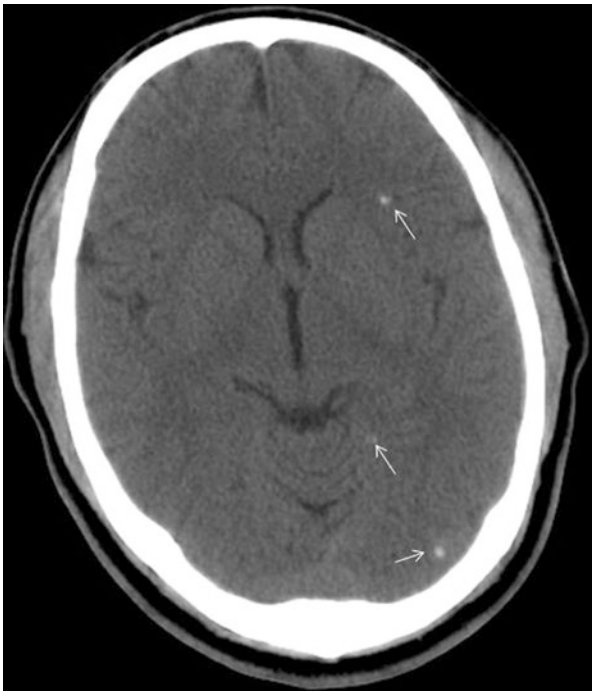

Fig. 23.6 Non-contrast head CT showing three calcified cysts in a patient with neurocysticercosis

cases, a scolex of the organism may be visible. CT is better suited for identifying calcified cysts. The diagnosis is confirmed by a positive serum enzyme-linked immunoelectrotransfer blot assay (EITB); lumbar puncture is not required.

Treat single active lesions with albendazole 15 mg/kg/d in two divided doses for 10–14 days with close infectious disease consultation [29]. Add praziquantel 50 mg/kg/d for patients with multiple active lesions. Be sure to pre-treat all patients who require anti-parasitic agents with corticosteroids to prevent life-threatening inflammation and cerebral edema which may occur as the organisms die. Anticonvulsants should be used for patients with seizures. Neurosurgical intervention may be needed to treat patients with severe mass effect and ventricular obstruction.

Tuberculoma

Tuberculosis of the CNS produces a wide variety of serious problems including seizures, headaches, strokes, and meningitis (Chap. 1). Hematogenous seeding of *Mycobacterium tuberculosis* may lead to an accumulation of organisms in the brain known as a tuberculoma. This is particularly common in patients from the Indian subcontinent and East Asia. The radiographic appearance of tuberculoma is quite variable: the most common appearance is a mass lesion with a T2-hypointense core and hyperintense rim, with approximately 2/3 of patients having more than one, sometimes numerous lesions [30]. Treatment of tuberculoma includes a four-drug regimen (isoniazid, pyrazinamide, rifampin, and either ethambutol or streptomycin) supervised by an infectious disease specialist. Lesions that produce severe mass effect may require neurosurgical intervention.

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Index

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