CHAPTER 103

Brain and Cranial Nerve Disorders

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This chapter discusses cranial nerve problems, cerebral venous thrombosis, and multiple sclerosis—neurologic disorders that often provide significant diagnostic and therapeutic challenges in management in the emergency department (ED) setting (Table 103-1).

TRIGEMINAL NEURALGIA

Perspective

Trigeminal neuralgia, or *tic douloureux*, is a syndrome featuring painful paroxysms in one or more distributions of the trigeminal nerve. Trigeminal neuralgia is relatively uncommon, with an annual incidence of 4 to 13 cases per 100,000 population.[1,2] It is more common in women than in men, with a female-to-male ratio of 1.7:1. Affected persons typically are between 50 and 69 years of age, and symptoms occur more frequently on the right side of the face.[3]

Pathophysiology

Trigeminal neuralgia is an idiopathic disorder, although significant evidence points to vascular compression of the trigeminal nerve root in many cases. This compression commonly is caused by a tortuous arterial or venous loop in the posterior fossa, an arteriovenous malformation, or rarely a tumor. In surgical case series, vascular compression of the trigeminal nerve root is found in 80 to 90% of cases.[4,5] Of note, however, structural lesions are not found in all patients with trigeminal neuralgia.[6]

Clinical Features

Trigeminal neuralgia manifests with unilateral facial pain, typically characterized as lancinating paroxysms of pain in the lips, teeth, gums, or chin. The pain of trigeminal neuralgia commonly is associated with physical triggers such as chewing, brushing the teeth, shaving, washing or touching the affected area of the face, swallowing, or exposure to hot or cold temperature in the affected area. The maxillary and mandibular divisions of the trigeminal nerve are most commonly involved; rarely, the ophthalmic division alone is involved. Patients tend to experience the pain in clustered episodes that last a few seconds to several minutes. The attacks can occur during the day or night but rarely arise during sleep.[6,7]

Diagnostic Strategies

A careful history and physical examination should be performed to rule out other painful facial conditions including odontogenic infections, sinus disease, otitis media, acute glaucoma, temporomandibular joint disease, and herpes zoster. Patients who lack local pathologic findings to explain the painful syndrome require a very careful neurologic examination. The presence of a neurologic deficit should prompt suspicion of a structural lesion, such as aneurysm, tumor, or other intracranial lesion such as from multiple sclerosis (MS). Of note, 2 to 4% of patients with trigeminal neuralgia also have MS.[8] Patients with normal findings on the head and neck examination and no neurologic deficits who have episodic, unilateral facial pain associated with nonpainful triggers are likely to have trigeminal neuralgia.

Management

Since the 1960s the medical treatment of choice for trigeminal neuralgia has been use of the anticonvulsant carbamazepine. The purported effectiveness of this treatment is, however, based on uncontrolled studies, and the mechanism of action of anticonvulsant therapy for trigeminal neuralgia is unclear. The true efficacy of medical therapy is difficult to assess owing to a very high rate of spontaneous remission. Nonetheless, carbamazepine appears to be an effective and well-tolerated agent for treatment of trigeminal neuralgia. The initial dosage of carbamazepine is 100 mg twice daily; this dose is then increased to three times daily after one week. The dose may be increased by 100 mg per day, up to a maximum of 1200 mg per day. A complete blood count and liver function studies should be performed periodically in these patients to monitor for hematologic and hepatic side effects. Additional agents that have been used for treatment of trigeminal neuralgia include phenytoin, baclofen, valproate sodium, lamotrigine, and gabapentin. None of these drugs have been shown to be more effective than carbamazepine.[7]

Surgical management has been a theraputic option since the 1950s. Surgical procedures include both peripheral approaches and central procedures. Peripheral strategies include medication injection and cryotherapy techniques designed to temporarily block, or permanently ablate, branches of the peripheral trigeminal nerve. Although these procedures are relatively effective initially, recurrence is common. Repeated nerve

Table 103-1 The Cranial Nerves: Normal Function and Pathologic Considerations

CRANIAL NERVE	CLINICAL FUNCTION RELEVANT TO EMERGENCY MEDICINE	PATHOLOGIC FEATURES	POSSIBLE CAUSES
Cranial nerve I: Olfactory nerve	Sense of smell	Unilateral anosmia	*Trauma*: Skull fracture or shear injury interrupting olfactory fibers traversing the cribriform plate *Tumor*: Frontal lobe masses compressing the nerve
Cranial nerve II: Optic nerve	Vision	Unilateral vision loss	*Trauma*: Traumatic optic neuropathy *Tumor*: Orbital compressive lesion *Inflammatory*: Optic neuritis (MS) *Ischemic*: Ischemic optic neuropathy
Cranial nerve III: Oculomotor nerve	Extraoculomotor function via motor fibers to levator palpebrae, superior rectus, medial rectus, inferior rectus, inferior oblique muscles Pupillary constriction via parasympathetic fibers to constrictor pupillae and ciliary muscles	Ptosis caused by loss of levator palpebrae function Eye deviated laterally and down Diplopia Dilated, nonreactive pupil Loss of accommodation	*Trauma*: Herniation of the temporal lobe through the tentorial opening causing compression and stretch injury to the nerve *Ischemic*: Especially in diabetes Microvascular ischemic injury to nerve causes extraocular muscle paralysis but usually is papillary-sparing (often painful) *Vascular*: Intracranial aneurysms may press on the nerve, leading to dysfunction Myasthenia gravis can lead to atraumatic ocular muscle palsy
Cranial nerve IV: Trochlear nerve	Motor supply to the superior oblique muscle	Inability to move eye downward and laterally Diplopia Patients tilt head toward unaffected eye to overcome inward rotation of affected eye	Trauma is the most common cause of nerve dysfunction
Cranial nerve V: Trigeminal nerve	Motor supply to muscles of mastication and to tensor tympani Sensory to face, scalp, oral cavity (including tongue and teeth)	Partial facial anesthesia Episodic, lancinating facial pain associated with benign triggers such as chewing, brushing teeth, light touch	*Trauma*: Facial bone fracture may injure one section, leading to area of facial anesthesia Tic douloureux
Cranial nerve VI: Abducens nerve	Motor supply to the lateral rectus muscle	Inability to move affected eye laterally Diplopia on attempting lateral gaze	*Tumor*: Lesions in the cerebellopontine angle Any lesion, vascular or otherwise, in the cavernous sinus may compress nerve *Elevated intracranial pressure (ICP)*: Because of its position and long intracranial length, increased ICP from any cause may lead to injury and dysfunction of the nerve
Cranial nerve VII: Facial nerve	Motor supply to muscles of facial expression Parasympathetic stimulation of the lacrimal, submandibular, and sublingual glands Sensation to the ear canal and tympanic membrane	*Hemifacial paresis*: *Lower motor neuron lesion* leaves entire side of face paralyzed *Upper motor neuron lesion* leaves forehead musculature functioning Abnormal taste Sensory deficit around ear Intolerance to sudden loud noises	*Lower motor neuron*: *Infection* (viral): The likely cause of Bell's palsy *Lyme disease*: The most common cause of bilateral cranial nerve VII palsy in areas where Lyme disease is endemic Bacterial infection extending from otitis media *Upper motor neuron*: Stroke, tumor
Cranial nerve VIII: Vestibulocochlear nerve	Hearing and balance	Unilateral hearing loss Tinnitus Vertigo, unsteadiness	*Tumors*: Acoustic neuroma Mimics Ménière's disease, perilymphatic fistula

Table 103-1 The Cranial Nerves: Normal Function and Pathologic Considerations—cont'd

CRANIAL NERVE	CLINICAL FUNCTION RELEVANT TO EMERGENCY MEDICINE	PATHOLOGIC FEATURES	POSSIBLE CAUSES
Cranial nerve IX: Glossopharyngeal nerve	General sensation to posterior third of tongue Taste for posterior third of tongue Motor supply to the stylopharyngeus	Clinical pathology referable to the nerve in isolation is very rare Occasionally painful paroxysms beginning in the throat and radiating down the side of the neck in front of the ear but behind the mandible	Brainstem lesion Glossopharyngeal neuralgia
Cranial nerve X: Vagus nerve	Motor to striated muscles and muscles of the pharynx, larynx, and tensor (veli) palatini Motor to smooth muscles and glands of the pharynx, larynx, thoracic and abdominal viscera Sensory from larynx, trachea, esophagus, thoracic and abdominal viscera	*Unilateral loss of palatal elevation*: Patients complain that on drinking liquids, the fluid refluxes through the nose *Unilateral vocal cord paralysis*: Hoarse voice	Brainstem lesion Injury to the recurrent laryngeal nerve during surgery
Cranial nerve XI: Spinal accessory nerve	Motor supply to the sternocleidomastoid and trapezius muscles	Downward and lateral rotation of the scapula and shoulder drop	Trauma to the nerve
Cranial nerve XII: Hypoglossal nerve	Motor supply to the intrinsic and extrinsic muscles of the tongue	*Tongue deviations*: *Upper motor neuron lesion* causes the tongue to deviate toward the opposite side *Lower motor neuron lesion* causes the tongue to deviate toward the side of the lesion, and the affected side atrophies over time	Stroke or tumor can cause upper motor neuron lesion Amyotrophic lateral sclerosis (ALS) can cause bilateral lower motor neuron lesion with atrophy Metastatic disease to the skull base may involve the nerve

blocks are not recommended owing to a high risk of permanent facial anesthesia.

Central procedures can be divided into percutaneous approaches and open approaches. Percutaneous destruction of the trigeminal ganglion can be done by means of radiofrequency ablation, thermal ablation, glycerol injection, or balloon microcompression. These procedures carry the risk of corneal anesthesia, oculomotor paresis, or masticatory weakness.[9]

Open surgical management is the surgical option of choice in most treatment centers. Open surgical procedures include microvascular decompression of the nerve with or without partial ablation. Although the open microvascular decompression procedure has proved to be very effective, with pain relief achieved in 80 to 95% of patients, the surgery is associated with the risk of significant complications, including hearing loss, facial anesthesia, cerebrospinal fluid leak, brainstem or cerebellar injury, headaches, meningitis, and death.[10,11] Gamma knife radiosurgery, a minimally invasive, precision-directed stereotactic radiosurgery, also has been associated with good outcomes. This highly specialized technique requires extremely sophisticated stereotactic radiofrequency equipment and is available only in specialized centers.[12,13]

Disposition

Patients with suspected trigeminal neuralgia should be referred for specialty evaluation. Patients with a neurologic deficit require urgent imaging studies, typically magnetic resonance imaging (MRI), to rule out a mass or vascular abnormality.

KEY CONCEPTS

- Patients with unilateral, intermittent, lancinating facial pain without abnormalities on physical examination are likely to have trigeminal neuralgia.
- Carbamazepine is the first-line agent for medical treatment.
- Patients who do not tolerate or whose pain is refractory to medical management may be candidates for microvascular decompression or ablation.

FACIAL NERVE PARALYSIS

Perspective

The acute onset of facial nerve paralysis often will prompt an ED visit, when early diagnosis and therapy can improve the patient's chance for recovery of function of the facial nerve. Facial nerve paralysis of acute onset affects approximately 20 to 25 persons per 100,000 population per year, without geographic, gender, or race predilection.[14,15]

Principles of Disease

The facial nerve innervates the muscles of facial expression and the muscles of the scalp and external ear, in addition to the buccinator, platysma, stapedius, stylohyoid, and posterior belly of the digastric muscles. The sensory portion of the nerve supplies the anterior two thirds of the tongue with taste and

sensation to portions of the external auditory meatus, soft palate, and adjacent pharynx. The parasympathetic portion supplies secretomotor fibers for the submandibular, sublingual, lacrimal, nasal, and palatine glands.[16]

The nerve originates from the pontomedullary junction of the brainstem. The nerve enters the internal auditory meatus with cranial nerve VIII. Within the temporal bone the facial nerve has four major branches: the greater and lesser superficial petrosal nerves, the nerve to the stapedius muscle, and the chorda tympani. The facial nerve exits the temporal bone at the stylomastoid foramen. The nerve then enters the parotid gland, where it divides to supply the muscles of facial expression.[16,17]

Pathophysiology

Although a complete list of possibilities in the differential diagnosis for facial nerve paralysis would be a long one, the causes pertinent to emergency medicine can be grouped into three specific categories: infectious, traumatic, and neoplastic.

Infection

Bell's Palsy

Bell's palsy, also commonly called *idiopathic facial paralysis*, has long been postulated to have a viral cause. This disease entity is characterized by an abrupt onset of a lower motor neuron paresis that can progress over 1 to 7 days to complete paralysis. A prodromal illness is described by 60% of patients. Symptoms and signs frequently associated with the facial paresis include ear pain, a perception of sensory change on the involved side of the face, decreased tearing, an overflow of tears on the cheek (epiphora), abnormally acute hearing (hyperacusis), and an impairment or perversion of taste (dysgeusia).[18]

Treatment approaches can be medical or surgical. The primary medical therapies for Bell's palsy center on reducing inflammatory changes to the nerve with corticosteroids and treating the presumed viral cause. If these therapies are unsuccessful then surgical decompression may be considered.

The use of corticosteroids for Bell's palsy has been controversial. The rationale for this application of steroid therapy is that edema of the nerve, confined within the facial canal, is thought to cause or contribute to the nerve injury. On the basis of this theory, most experts currently recommend a course of prednisone with an initial dose of 1 mg/kg per day for 7 to 10 days, with or without a short taper.[14,17,19,20] The most definitive randomized, double-blind, placebo-controlled trial involving 496 patients showed an improvement in complete recovery of facial nerve function at 3 months from 64% with placebo to 83% with the use of prednisolone in a dose of 25 mg by mouth twice daily.[21] Therapy should be started as soon as possible, ideally within the first 24 hours, but is still recommended for patients without contraindications who seek treatment within 1 week of symptom onset.[19]

A number of publications have advanced the belief that Bell's palsy may be caused by herpesvirus infection. One study demonstrated herpes simplex virus type 1 DNA in the endoneural tissue of 11 of 14 patients with Bell's palsy but not in that of control subjects.[22] In a trial of prednisone and acyclovir in 99 patients, patients treated with prednisone and acyclovir had a more favorable recovery than that observed in patients receiving prednisone alone.[23] A study of 296 patients with Bell's palsy treated with valacyclovir or placebo in addition to a fixed dose of prednisolone found significant benefit to the addition of valacyclovir, particularly in the setting of severe palsy or in those treated within 24 hours of symptom onset.[24] Other studies have found conflicting results. Despite a lack of overwhelming evidence, the addition of an antiviral agent should be considered in the treatment of Bell's palsy, especially with severe loss of function. The most commonly recommended antiviral regimens include valacyclovir, 1000 mg orally two times daily for 10 days. Valacyclovir and famciclovir have better oral absorption, are better tolerated, and are dosed less frequently, resulting in higher compliance. Accordingly, they have been recommended as alternatives to acyclovir.[17,19,20,22,25] As with steroid therapy, although earlier treatment is preferred, treatment should be considered for patients presenting within 1 week of symptom onset.

Ramsay Hunt Syndrome

Ramsay Hunt syndrome (herpes zoster oticus) is characterized by unilateral facial paralysis, a herpetiform vesicular eruption, and vestibulocochlear dysfunction. The vesicular eruption may occur on the pinna, external auditory canal, tympanic membrane, soft palate, oral cavity, face, and neck as far down as the shoulder. The pain is considerably more severe than that associated with Bell's palsy, and it frequently is out of proportion to physical findings. In addition, outcomes are worse than with Bell's palsy, with a lower incidence of complete facial recovery and the possibility of sensorineural hearing loss. Therapy is similar to that for Bell's palsy. Both prednisone and antiviral therapy for 7 to 10 days are advocated.[17,26,27]

Lyme Disease

Lyme disease is the most frequent vector-borne infection in the United States. It is caused by the spirochete *Borrelia burgdorferi* and is spread by the bite of *Ixodes* genus ticks. Neurologic manifestations can arise in any phase of the disease, and the incidence of facial palsy in patients with neurologic involvement is 35 to 51%. In regions in which Lyme disease is endemic, it has been shown to be the leading cause of facial paralysis in children, responsible for one half of all pediatric cases of facial nerve paralysis.[28,29]

Bilateral facial nerve paralysis is rare but can occur with systemic infections. The two diseases most commonly associated with bilateral simultaneous onset of facial paralysis are Lyme disease and infectious mononucleosis. Bilateral facial paralysis should be considered to be a manifestation of Lyme disease until further testing excludes this diagnosis.[20,28–30] The evaluation and treatment of Lyme disease are discussed in Chapter 132.

Bacterial Infections

Facial paralysis can be caused by acute bacterial infections of the middle ear, mastoid, or external auditory canal. In the preantibiotic era, facial paralysis was associated with acute otitis media in approximately 2% of cases; today, however, it occurs in only 0.2% of cases. Treatment consists of intravenous antibiotics and myringotomy for decompression. Malignant otitis externa can be associated with facial paralysis. This disease entity is most commonly seen in immunocompromised patients and usually is caused by *Pseudomonas* infection. Treatment involves prolonged intravenous antipseudomonal antibiotic therapy and may require surgical débridement.[20,31]

Trauma

In patients with head trauma, the facial nerve is the most commonly injured cranial nerve. The cause generally is a temporal bone fracture with nerve transection. Surgical exploration is warranted if there is firm evidence that the nerve has been transected, indicated by a sudden onset of complete unilateral facial paralysis, loss of electrical activity, and evidence of a displaced fracture involving the facial canal.

Neoplasm

Tumors of the facial nerve itself, or tumors anywhere along the course of the facial nerve that invade or compress the nerve, may lead to facial paralysis. Typically the course is progressive over at least 3 weeks. A sudden onset of paralysis, however, does not rule out an underlying tumor, because facial paralysis secondary to a neoplasm is of sudden onset in approximately 25% of cases.[32] A neoplastic cause should be suspected in patients who suffer from recurrent ipsilateral facial paralysis, significant pain, prolonged symptoms, or any other concomitant cranial nerve abnormality.

Clinical Features and Differential Considerations

The medical history should focus on onset of the paralysis, concentrating on timing and rapidity of onset and looking for any associated signs and symptoms. A rapid onset of facial paralysis with dysgeusia and hyperacusis preceded by a viral prodrome is suggestive of Bell's palsy. A history of recurrent ipsilateral paralysis or slow progression of symptoms is more characteristic for a tumor. Associated cranial nerve abnormalities, although occasionally seen with Bell's palsy, also point to the possibility of a tumor or ischemic insult. The Ramsay Hunt syndrome causes significant pain and a vesicular rash, although the rash may follow the facial paresis by a few days. Significant anatomic abnormalities on visual or otoscopic inspection of the ipsilateral ear will be found with bacterial otitis media and otitis externa. Finally, systemic symptoms or bilateral facial paresis, especially in endemic areas, should raise the possibility of Lyme disease.

Diagnostic Strategies

The diagnostic workup of acute facial nerve paresis is based on whether the clinical picture is suggestive of a disease process other than Bell's palsy. If the clinical history is classic for Bell's palsy, then no imaging or laboratory studies are required. Of note, any history of possible exposure warrants serologic evaluation for Lyme disease. Although outpatient testing including electroneurography may ultimately be performed, this usually is not part of the initial evaluation.

The physical examination finding of a "central" seventh nerve paralysis (upper face–sparing) should prompt imaging with computed tomography (CT) or MRI, and consideration should be given to the possibility of an acute stroke or other hemispheric lesion. History or physical examination findings suggestive of a possible tumor require imaging to rule out a neoplasm. The study of choice will depend on the institution and preferences of the consultant.

Disposition

The vast majority of patients who have a seventh nerve paralysis will have a clinical diagnosis of Bell's palsy and may be discharged with referral for short-term follow-up. Patients with a possible hemispheric process such as stroke or tumor should be hospitalized for further evaluation. Patients suspected of having Lyme disease require immediate initiation of appropriate antibiotic therapy.

In patients with a peripheral facial nerve paralysis, the ipsilateral eye should be patched, and consideration should be given to ophthalmologic follow-up, because there is a high rate of corneal abrasions and corneal dryness associated with the inability to properly blink or completely close the eye.

KEY CONCEPTS

- Recent literature highlights significant potential benefit for patients with clinical evidence of Bell's palsy when they are treated early in the course with corticosteroids. The additional benefit of adding antiviral medication is controversial, but this treatment probably is warranted in patients with severe loss of function.
- Slowly progressive facial paralysis is suggestive of a neoplasm. Recurrent unilateral paralysis may occur with Bell's palsy but frequently (30%) is seen in patients with tumor.
- Simultaneous bilateral facial paralysis is suggestive of Lyme disease, which must be considered as a possible cause, especially in endemic regions.
- Patients who have facial muscle paresis with intact forehead movement should be considered to have an upper motor neuron lesion until the diagnostic investigation proves otherwise.

VESTIBULAR SCHWANNOMA

Perspective

Vestibular schwannoma, formally referred to as *acoustic neuroma*, is a rare but important cause of sensorineural hearing loss. The annual incidence of VS is 1 case per 100,000 population, with a mean age at the time of detection of 46 to 58 years.[33] The female-to-male ratio is 1.5:1. Vestibular schwannoma is very rarely bilateral, occurring in this form in approximately 5% of cases and generally associated with type II neurofibromatosis. Although histologically benign, vestibular schwannoma can cause neurologic damage by direct compression on the eighth cranial nerve and the other structures in the cerebellopontine angle.[34]

Principles of Disease

Vestibular schwannoma arises from the Schwann cells covering the vestibular branch of the eighth cranial nerve as it passes through the internal auditory canal. The tumor may compress the cochlear (acoustic) branch of the eighth cranial nerve, causing hearing loss, tinnitus, and dysequilibrium. Continued growth of the tumor may result in compression of structures in the cerebellopontine angle, where the facial and trigeminal nerves may be compressed and damaged. Larger tumors may further encroach upon the brainstem and if large enough may compress the fourth ventricle, ultimately resulting in signs of increased intracranial pressure (ICP).[35]

Clinical Features

Asymmetrical sensorineural hearing loss is the hallmark of vestibular schwannoma. Up to 15% of patients with this tumor, however, will have normal results on an audiogram. These patients typically have symptoms such as unilateral tinnitus, imbalance, headache, fullness in the ear, otalgia, or facial nerve weakness. Thus, patients with asymmetrical symptoms should be further evaluated for vestibular schwannoma even with normal findings on the audiogram.[36]

Vestibular schwannomas are extremely slow-growing tumors, averaging an approximately 1-mm increase per year, although many do not grow at all on serial examinations.[37] Symptom onset is therefore generally quite gradual. In one series of 126 cases, the average time from symptom onset to discovery of a vestibular schwannoma was approximately 4 years.[38]

Diagnostic Strategies

When vestibular schwannoma is suspected, the patient should be evaluated with an audiogram or a gadolinium-enhanced MRI. This imaging technique is extremely sensitive and has led to earlier diagnosis and a decrease in mean size at detection of vestibular schwannoma. CT lacks the necessary sensitivity in the posterior cranial fossa to reliably rule out the presence of vestibular schwannoma. The smaller the tumor at the time of diagnosis, the more options there are for therapy and the better the potential prognosis.[34]

Differential Considerations

A majority of disease entities included in the differential diagnosis for acoustic neuroma cause symmetrical sensorineural hearing loss. Asymmetrical sensorineural hearing loss has few causes other than vestibular schwannoma. Ménière's disease may present a diagnostic dilemma because it can be asymmetrical. Ménière's disease may be differentiated from vestibular schwannoma in that the tinnitus of Ménière's disease usually is intermittent, whereas the tinnitus of vestibular schwannoma typically is continuous. In addition, patients with Ménière's disease typically describe true vertigo, whereas patients with a vestibular schwannoma are more likely to describe imbalance or dysequilibrium.

Vestibular schwannomas account for 80% of all cerebellopontine angle tumors. Among all other lesions, meningioma is the most common. Meningiomas more frequently cause symptoms of facial palsy or trigeminal nerve abnormality. Of note, however, considerable similarity between the clinical picture of a meningioma and that of vestibular schwannoma in the cerebellopontine angle has been described.[39]

Management

Vestibular schwannoma may be removed surgically or ablated with stereotactic radiation. In general, tumors larger than 3 cm are recommended for microsurgery, because radiation treatments, such as with the Gamma Knife or linear accelerator, are less effective for local control and growth arrest in larger masses. Smaller tumors are amenable to use of stereotactic radiation, which may have greater salvage rates of facial nerve function and hearing. Stereotactic radiation therapy generally has good long-term outcomes of local growth arrest, with nerve salvage approaching 90% or greater. Injuries to the trigeminal, facial, and acoustic nerves, and to the cerebellum, are possible complications of both procedures. In patients who are minimally symptomatic with small tumors, serial monitoring with MRI is a viable nonsurgical option. All patients should be evaluated by a specialist in the evaluation and treatment of vestibular schwannoma, because smaller tumor size at detection is associated with a better long-term outcome.[33,37]

Disposition

Patients with suspected acoustic neuroma should be referred for an audiogram or MRI and evaluation by a specialist in either otolaryngology or neurosurgery.

■ DIABETIC CRANIAL MONONEUROPATHY

Perspective

Cranial mononeuropathies occur uncommonly, usually are a complication of diabetes, and most often affect the extraocular muscles. The oculomotor nerve is most commonly affected, followed in order by the trochlear and abducens nerves. In one large series in Japan, the incidence of cranial nerve palsies was 1.0% among diabetics and 0.1% among nondiabetics.[40,41] Whereas ophthalmoplegia appears to be closely related to diabetes, facial palsy is less strongly correlated with this disease.[40]

KEY CONCEPTS

- The onset of unilateral auditory symptoms, especially sensorineural hearing loss, requires evaluation and referral to an ear, nose, and throat specialist.
- Neurologic symptoms of lower cranial nerve dysfunction, ataxia, or raised ICP may be caused by a benign tumor of the cerebellopontine angle.
- The smaller the tumor at diagnosis, the better the long-term outcome with definitive treatment.

Principles of Disease

The pathologic basis of diabetic mononeuropathy appears to be ischemia of the affected cranial nerve caused by occlusion of an intraneural nutrient artery serving the nerve. This occlusion leads to injury located primarily in the center of the nerve, because the core fibers are more dependent on the supply from such nutrient arteries. The peripheral fibers are less affected because they also are supplied by collateral vessels. In the oculomotor nerve, the preservation of the circumferentially located parasympathetic fibers explains the pupillary sparing that usually is found in this syndrome. In two studies, the microvascular changes in the intraneural arteries that lead to occlusion were noted in diabetic patients but absent in nondiabetics.[42,43]

Clinical Features

Patients typically describe acute onset of unilateral retro-ocular and supraorbital pain, diplopia, and ptosis.[41] The physical manifestations of a third cranial nerve palsy include the inability to move the eye superiorly and medially, accompanied by ptosis. The pupillary light reflex usually is present. Although a less common finding, the fourth and sixth cranial nerves may be affected. Patients with a fourth cranial nerve palsy are unable to move the eye inferolaterally, and those with a sixth cranial nerve palsy are unable to move the eye laterally. Because of the long intracranial course of the sixth nerve, a patient with an isolated sixth nerve palsy should be evaluated for an intracranial lesion or increased ICP.[44]

Differential Considerations

Evaluating cranial nerve dysfunction requires a thorough history and physical examination and cranial imaging, usually with MRI. Diabetic mononeuropathy should be considered a diagnosis of exclusion, with considerations in the differential diagnosis including trauma, tumor, vertebrobasilar ischemia, aneurysm, and hemorrhage into the brainstem.[45]

Management

Treatment consists of patching the affected eye and administration of analgesics and antiplatelet therapy. The prognosis is good. If the neuropathy does not begin to resolve within 3 to 6 months, or if more than one nerve is affected, another cause should be sought. Complete resolution is expected within the first year. Antioxidant preparations, including α-lipoic acid, have been used therapeutically and have not shown harm, but

such agents have yet to be shown to have convincing clinical effect.[46]

KEY CONCEPTS

- Diabetic neuropathy is a diagnosis of exclusion because no definitive diagnostic testing is available.
- Both ischemic and hemorrhagic brainstem lesions must be ruled out in the case of an acute ophthalmoplegia.
- Extraocular mononeuropathy is sufficiently common in patients with diabetes mellitus that its occurrence in isolation warrants evaluation of the patient for previously undiagnosed diabetes.

CEREBRAL VENOUS THROMBOSIS

Perspective

No precise studies of the epidemiology of cerebral venous thrombosis (CVT) have been performed. In case series, the median patient age is approximately 37 years, with a female-to-male ratio of 3:1.[47]

Principles of Disease

Cerebral blood is drained by several major veins that lead into the dural sinuses. The major dural sinuses are the superior sagittal sinus, the inferior sagittal sinus, the straight sinus, the lateral sinuses, and the sigmoid sinuses. The variability in symptoms and signs in patients who present with CVT stems from differences in thrombus location and acuity of thrombus formation. Symptoms of intracranial hypertension are present in most patients with sinus thrombosis, whereas those with thrombosis of the cerebral veins are thought to be more prone to hemorrhagic infarction and localizing neurologic deficits.[48] As with venous thrombosis in other locations, multiple causes and predisposing factors for CVT are recognized. Underlying causes often are divided into infectious and noninfectious categories. Infectious causes include local infections, such as sinusitis, otitis media, cellulitis on the face, and systemic infections. Noninfectious causes include direct injury to the cerebral venous system from trauma, surgery, tumor, dehydration, or any other condition that may predispose the patient to development of a hypercoagulable state.[49]

Clinical Features

The symptoms and signs associated with CVT are quite varied. Headache is the primary feature of CVT in 74 to 92% of affected patients.[49,50] Papilledema is noted in 28 to 45% of cases.[47,50,51] Lethargy, decreased level of consciousness, or mental status changes may be noted. Seizures occur in 35 to 50% of patients in the acute phase.[47,49,51] In addition to the location and acuity of thrombosis formation, a patient's symptom onset will vary in accordance with the extent of collateral vessel growth in the venous territory. Early thrombotic changes may be well compensated for by the collateral venous drainage. Symptoms will appear only when the compensation for venous thrombosis is no longer sufficient. Variability in collateralization between patients also adds to the variability and time course of symptomatology. Two national and international observational studies document an average time from symptom onset to diagnosis of 7 days, reflecting the difficulty in diagnosing this rare disease entity.[47,51,52] The reported incidence of focal neurologic signs, including seizures, on clinical examination varies between series, ranging from 25 to 71%.[49,50] Because of the broad spectrum of possible clinical features, the diagnosis of CVT may be difficult but should be a consideration in any patient with unexplained headache, especially in combination with focal neurologic deficit, papilledema, or seizures.

Diagnostic Strategies

The gold standard modality for the diagnosis of CVT has shifted in recent years from cerebral angiography to magnetic resonance venography (MRV). CT scanning is useful in the initial workup of the patient with possible CVT, but noncontrast CT is neither sensitive nor specific enough to reliably confirm or exclude the diagnosis. Findings on CT that are consistent with CVT include hyperdensity of a thrombosed sinus, brain edema, and hemorrhage secondary to venous congestion. CT venography is both more sensitive and more specific in diagnosing CVT.

Similar to CT scanning, MRI also can demonstrate local changes secondary to venous congestion, such as brain edema or hemorrhage. In addition, MRI can demonstrate the possibility of CVT based on the lack of a "flow void." On conventional MRI, a flow void indicates the presence of blood flow within the sinus, whereas the absence of a flow void indicates a possible thrombus. Diagnostic accuracy, however, is greatly improved through use of MRV. This technique takes advantage of the MRI signal characteristics of flowing blood to create images of venous structures. Combining these imaging techniques further enhances diagnostic accuracy. For imaging a particular dural sinus, presence of the sinus on conventional MRI and lack of flow on MRV are diagnostic of a sinus thrombosis. This combined approach has diagnostic sensitivity similar to that of conventional angiography.[49,53]

Two small studies show similar sensitivity between MRV and CT venography for the diagnosis of CVT when the CT study is performed on a multidetector row CT scanner. Both studies, involving a total of 69 patients, showed 100% sensitivity of CT venography for CVT in comparison with MRV.[54,55] The sensitivity of CT venography performed by scanners that do not use multidetector row technology is unknown.

Several small studies have attempted to evaluate the usefulness of the D-dimer assay as a screening tool to exclude CVT, particularly when MRI or CT venography is not available. Although the reported sensitivity rates are fair at 83 to 100%, larger prospective studies need to be done to further define the role of D-dimer in the evaluation of CVT, because several case reports have noted normal D-dimer levels in the setting of documented CVT.[56-59] In general, although a normal D-dimer level does not exclude the diagnosis of CVT, it does appear to make this diagnosis much less likely, particularly in a patient with symptoms of less than 2 weeks in duration.

Differential Considerations

Considerations in the differential diagnosis of CVT include the conditions that cause patients to present with the new onset of neurologic deficits, alteration in consciousness, or severe headache. A diagnosis of CVT should be considered in a patient with such symptoms when the etiology is unclear, presence of having a hypercoagulable state is likely, and the head CT scan is normal in appearance or shows subtle signs of CVT.

Management

CVT is a relatively rare disease, and controlled studies evaluating its treatment are lacking. Current therapeutic consensus

strongly recommends systemic anticoagulation with low-molecular-weight or unfractionated heparin to prevent further clot formation and to promote recanalization, even in patients with intracranial hemorrhage on initial imaging.[49,50,60,61] In one placebo-controlled randomized trial comprising 20 patients, anticoagulation with heparin to a target partial thromboplastin time (PTT) of 80 to 100 seconds demonstrated benefit, even in patients in which evidence of intracranial hemorrhage was seen on the CT scan before anticoagulation.[62] In another study of 60 patients randomized to receive placebo or low-molecular-weight heparin, no statistical benefit was shown for treatment.[63] Two large observational trials showed improvement in modified Rankin scale at follow-up in the anticoagulated groups, although the trials were not randomized.[47,51] Despite a paucity of randomized controlled trials, expert opinion favors anticoagulation in all groups unless another contraindication is present.[64]

Catheter-based intervention with thrombolysis has been attempted in multiple case series using either urokinase or tissue plasminogen activator. Thrombolysis was shown to be relatively safe and relatively successful in very small case series.[61] In one nonrandomized study of 40 patients, 20 received systemic heparin and 20 received catheter-based infusion of urokinase followed by systemic heparin. Despite initially worse neurologic function in the thrombolysis group, a significant difference in neurologic function favoring thrombolysis was observed at discharge.[65] Although this therapy is promising, it should be considered only for patients with symptoms of decreased level of consciousness, elevated ICP, or rapid deterioration on neurologic examination.

Disposition

All patients with suspected CVT should be admitted to a unit capable of providing a high level of care with neurologic consultation. Patients should be anticoagulated if no contraindication exists, and catheter-based thrombolysis should be considered in patients with depressed mental status or focal findings on neurologic exam.

KEY CONCEPTS

- CVT is a relatively rare entity, and only awareness of and familiarity with the clinical presentation will lead to the correct diagnosis.
- The onset may be insidious with a considerable delay between onset and arrival in the treatment setting.
- The differential diagnosis for CVT should consider other conditions that cause patients to present with new-onset neurologic deficits, alteration in consciousness, or severe headache. CVT is more likely to be present in such patients when the etiology is unclear, the patient is suspected of having a hypercoagulable state, and the head CT is normal in appearance or shows subtle signs of CVT.
- Noncontrast CT scanning is not adequate to rule out CVT. An MRI with MRV is recommended, although multidetector row CT venography is an acceptable alternative.
- Treatment of most patients with CVT should include systemic anticoagulation, even in the setting of hemorrhagic cerebral infarcts, unless another contraindication exists.

MULTIPLE SCLEROSIS

Perspective

Multiple sclerosis (MS) is an inflammatory disease that affects the central nervous system (CNS). Although the exact etiology remains uncertain, the pathologic manifestation of this inflammatory disease is a demyelination of discrete regions (plaques) within the CNS with a relative sparing of axons. The clinical picture is highly variable but is classically characterized by episodes of neurologic dysfunction that evolve over days and resolve over weeks.

MS has an overall prevalence in the United States of 0.1%. The peak age at onset is 25 to 30 years, with women being slightly younger at onset than men. The incidence in women exceeds that of men by a ratio of 1.8 : 1. The worldwide prevalence is greatest in the United Kingdom, Scandinavia, and North America. Epidemiologic studies indicate that both genetic and environmental factors are associated with an increased incidence of this disease. MS has a 30% concordance rate between monozygotic twins, and 20% of patients with MS have at least one affected relative. MS is more common in temperate climates. It is rare between 23 degrees north and south latitudes but has a rising incidence above and below 50 degrees north and south latitudes, respectively. Although no exact environmental factor has been identified, if a person emigrates from an area of high prevalence to an area of low prevalence before the age of 20, the risk is diminished. MS is rare in Africans and Asians, but African Americans have a higher incidence than their relatives who remain in Africa.[66] In addition, reports of clusters or miniepidemics support environmental factors. Thus, an environmental cause superimposed on genetic susceptibility appears to be a likely etiologic scenario.[67,68]

Principles of Disease

MS is considered to be an organ-specific autoimmune disease. One theory proposes that genetic factors interact with an environmental trigger or infection to establish pathologically autoreactive T cells in the CNS. After a long and variable latency period (typically 10 to 20 years), a systemic trigger, such as a viral infection or superantigen, activates these T cells. The activated T cells, on reexposure to the autoantigen, initiate the inflammatory response. This sets off a complex immunologic cascade that leads to the demyelination characteristic of MS. This demyelination process releases CNS antigens that are hypothesized to initiate further episodes of autoimmune-induced inflammation. The mechanisms underlying this autoimmunity in MS are unknown.[69]

Clinical Features

The clinical picture in MS is one of marked heterogeneity. The classic clinical syndrome consists of recurring episodes of neurologic symptoms that rapidly evolve over days and slowly resolve. Variability occurs in age at onset, location of CNS lesions, frequency and severity of relapses, and the degree and time course of progression.

The clinical features of MS can be divided into areas of specific CNS impairment: cognition, cranial nerves, motor pathways, sensory pathways, cerebellar pathways, and bowel, bladder, and sexual dysfunction.[66]

Patients with MS have frequent complaints of poor memory, distractibility, and a decreased capacity for sustained mental effort. Formal neuropsychological testing suggests that cognitive involvement is common and underreported. Specifically,

neuropsychological testing has shown that 43 to 65% of patients with MS have some degree of cognitive impairment.[70,71] Of note, a correlation has been found between the MRI-based total lesion load and presence of cognitive impairment.[72]

Cranial nerve dysfunction is common in MS. The most common associated cranial nerve abnormality is *optic neuritis*, a unilateral syndrome characterized by pain in the eye and a variable degree of visual loss affecting primarily central vision. Within 2 years of an attack of optic neuritis, the risk of MS is approximately 20%, and within 15 years, it is approximately 45 to 80%.[73,74] Optic neuritis often is the first symptom of MS.[75,76]

As a result of lesions in the vestibulo-ocular connections, the oculomotor pathways also may be affected. The deficit may manifest as diplopia or nystagmus. The nystagmus may be severe enough that the patient may complain of oscillopsia (a subjective oscillation of objects in the visual field). Cranial nerve impairment also may include impairment of facial sensation, which is relatively common. Unilateral facial paresis also may occur. In addition, the occurrence of trigeminal neuralgia in a young person may be an early sign of MS.

Motor pathways also are commonly involved. Specifically, corticospinal tract dysfunction is common in patients with MS. Paraparesis or paraplegia is all too common and occurs with greater frequency than upper extremity lesions, owing to the common occurrence of lesions in the motor tracts of the spinal cord. In patients with significant motor weakness, spasms of the legs and trunk may occur on attempts to stand from a seated position. This dysfunction is manifested on physical examination as spasticity that typically is worse in the legs than in the arms. The deep tendon reflexes are markedly exaggerated, and sustained clonus may be demonstrated. Although these symptoms frequently are bilateral, they generally are asymmetrical.[66]

Sensory manifestations are a frequent initial feature of MS and will be present in nearly all patients at some point during the course of the disease. Sensory symptoms are commonly described as numbness, tingling, "pins and needles" paresthesias, coldness, or a sensation of swelling of the limbs or trunk.[66]

Impairment of the cerebellar pathway results in significant gait imbalance, difficulty with coordinated actions, and dysarthria. Physical examination reveals the typical features of cerebellar dysfunction, including dysmetria, dysdiadochokinesis (an impairment of rapid alternating movements), a breakdown in the ability to perform complex movements, an intention tremor in the limbs and head, truncal ataxia, and dysarthria.[66]

Impairment of bowel, bladder, and sexual function also is common. The extent of sphincter and sexual dysfunction usually parallels the motor impairment in the lower extremities. Urinary frequency may progress to urinary incontinence with progression of the disease. An atonic bladder may develop, which empties by simple overflow and often is associated with the loss of perception of bladder fullness and with anal and genital hypoesthesia. Constipation becomes common over time, and almost all patients with paraplegia require special measures to maintain effective bowel habits. Sexual dysfunction, although frequently overlooked, is very common in MS. Approximately 50% of patients become completely sexually inactive as a result of this disease.[66]

Diagnostic Strategies

Although no laboratory tests are diagnostic for MS, one clinical feature remains relatively unique to this disease: *Uhthoff's phenomenon*, temporary worsening of current or preexisting signs or symptoms of MS secondary to small increases in the patient's body temperature. Accordingly, exercise, a hot bath, exposure to a warm environment, or fever can bring about Uhthoff's phenomenon. This phenomenon reflects subclinical demyelination or preexisting injury to nerves without obvious significant clinical involvement before heat exposure or temperature elevation.[66]

The clinical diagnosis rests on occurrence of at least two clinical episodes with different neurologic symptoms at different times. Thus, MS commonly has been characterized as a disorder with lesions that differ in time and space. It also has been described as a relapsing-remitting disorder with symptoms that fluctuate over time.

Findings on cerebrospinal fluid (CSF) analysis are abnormal in 90% of the cases. Fifty percent of patients will have pleocytosis, with more than 5 lymphocytes per high-power field in the CSF. Approximately 70% of patients will have an elevated gamma globulin level, with immunoglobulin G (IgG) ranging from 10 to 30% of the CSF total protein. Electrophoresis of the CSF demonstrates oligoclonal bands of IgG in 85 to 95% of patients who carry a diagnosis of MS; however, oligoclonal bands of IgG also are seen with neurosyphilis, fungal meningitis, and other CNS infections. Lumbar puncture should be considered for all patients with suspected MS, but mass lesions and elevated ICP should be ruled out before lumbar puncture.[77]

The initial imaging test to aid in the diagnosis of multiple sclerosis is MRI. MRI is a sensitive test for the detection of lesions consistent with MS and also is useful to assess disease severity.[78] The lesions of MS typically appear hyperintense, or bright white, on T_2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI studies. Lesions usually are multiple and commonly are found in the periventricular white matter.[79] In patients with an initial neurologic event consistent with CNS demyelination and an MRI cranial study showing multiple white matter lesions, the 5-year risk of developing MS is 60%. Patients with similar clinical syndromes and a normal MRI appearance have less than a 5% 5-year risk.[80]

Differential Considerations

Other diseases that affect the CNS white matter may be clinically and radiographically similar to MS. Considerable care must be taken to exclude these disease processes before making a diagnosis. These include CNS tumors (especially lymphomas and gliomas), spinal cord compression, vasculitides, Behçet's disease, neurosarcoidosis, postinfectious and postvaccinal encephalomyelitis, human immunodeficiency virus (HIV) encephalopathy, Lyme disease, and vitamin B_{12} deficiency.

Management

Management of patients with MS has essentially three aspects: (1) therapies aimed at halting the progression of the disease, (2) treatment for acute exacerbations, and (3) therapies designed to modify complications.

Therapies aimed at halting disease progress are based primarily on the use of either β-interferon or glatiramer acetate. The interferons are a group of natural compounds with antiviral and immunomodulatory actions, which are retained by the recombinant preparations used in therapy for MS, interferon beta-1a and interferon beta-1b. Side effects include flulike symptoms, depression, anxiety, and confusion. In one study, 560 patients with MS were randomly assigned to receive subcutaneous interferon beta-1a or placebo ($n = 187$) three times a week for 2 years. The relapse rate was significantly lower at 1 and 2 years with interferon beta-1a than with placebo. The time to first relapse was prolonged significantly and the accu-

mulation of brain lesions on MRI was lower in the treatment group than in the placebo group. The investigators concluded that subcutaneous interferon beta-1a is a well-tolerated and effective treatment for relapsing-remitting MS in terms of relapse rate, defined disability, and all MRI outcome measures.[81] β-Interferon also has been shown to retard progression to clinically definite MS and to decrease the total number of brain lesions seen on subsequent MRI studies in patients who have their first demyelinating episode with MRI abnormalities at initial presentation.[82-85] This finding highlights the importance of early evaluation and treatment.

Glatiramer acetate also has successfully been used in the treatment of MS. This agent is a mixture of synthetic polypeptides designed to mimic myelin basic protein. The mechanism of action by which glatiramer acetate exerts its effect is unknown, but it is thought to modify the immune processes responsible for the pathogenesis of MS. In one study, 251 patients with relapsing-remitting MS were randomized to receive daily subcutaneous injections of glatiramer acetate (previously called copolymer 1) or placebo for 24 months. Patients receiving glatiramer acetate experienced significantly fewer relapses and were more likely to demonstrate neurologic improvement, whereas those receiving placebo were more likely to worsen. This drug generally is quite well tolerated.[86]

Current recommendations for management of relapsing-remitting MS are to initiate treatment with β-interferon or glatiramer acetate. Such regimens have been demonstrated to decrease the volume of plaques seen on MRI and to diminish relapses.[69] Immunosuppressive agents, including mitoxantrone and azathioprine, also have been shown to be effective in reducing progression of disease but, in view of concerns over side effects, generally are used as second-line agents.[87,88]

Acute exacerbations of MS also should be targets for therapy. Although most such episodes will resolve without therapy, steroids have been demonstrated to diminish the duration of acute exacerbations. More than 85% of patients with relapsing-remitting MS show improvement with intravenous methylprednisolone. Intravenous steroids have been shown in controlled trials to speed the recovery from the visual loss of optic neuritis when compared with placebo. In addition, when patients with acute optic neuritis are treated with high-dose intravenous steroids, the 2-year rate of development of MS is reduced, although this effect diminishes over time.[74,89] Of interest, oral prednisone was not found to be helpful in the optic neuritis trials and was associated with a potential increase in the number of optic neuritis episodes.

The current standard therapy for an acute exacerbation in MS is intravenous methylprednisolone. A typical dose administered intravenously is 250 to 500 mg every 12 hours for 3 to 7 days. Whether this should be followed by an oral prednisolone taper remains controversial. Potential adverse effects of methylprednisolone therapy include fluid retention, gastrointestinal hemorrhage, anxiety, psychosis, infection, and osteoporosis.

Several therapies directed toward the complications of MS may be helpful. The associated spasticity generally is treated with baclofen. This is a highly effective therapy aimed at reducing the painful flexor and extensor spasms. A major side effect is drowsiness, which generally diminishes with continued use. Higher-dose therapy can cause confusion, especially in the setting of baseline cognitive impairment. For patients with intractable spasticity, baclofen is available for intrathecal administration by either bolus therapy or continuous implanted pump therapy. Additional therapeutic agents for control of spasticity include tizanidine, diazepam, and dantrolene.

The tremor and ataxia associated with MS occasionally are treated with propranolol, diazepam, or clonazepam. The results of these therapies, however, generally are unsatisfactory. Pain often is associated with MS and affects the shoulders, pelvic girdle, and face. The facial pain may be indistinguishable from that of trigeminal neuralgia. Treatment options include carbamazepine, baclofen, and tricyclic antidepressants. Fatigue, which is common, may be ameliorated with amantadine. This agent produces partial relief for a minority of patients. In controlled studies, the effect is only slightly better than placebo.[69]

Disposition

Patients with a history of MS who seek treatment for significant symptoms must first be evaluated to rule out other, non–MS-related pathology. Also, the presence of other systemic illnesses, especially infections, which can worsen the symptoms of MS, should be excluded. If the problem is thought to be an exacerbation of MS, most patients will require hospital admission for intravenous steroid therapy. An alternative to hospitalization may be to initiate intravenous steroids in the ED and to arrange for a next-day follow-up visit with the primary care physician or neurologist if outpatient intravenous steroid administration is an option.

Patients with the new onset of symptoms suggestive of MS should be admitted or referred to a neurologist, depending on the type and severity of symptoms.

KEY CONCEPTS

- Any patient with a long-term illness, such as MS, must be evaluated to rule out pathologic processes not related to that illness before an exacerbation of the illness can be assumed to be the cause of any problems experienced by the patient.
- Therapy for patients with MS will require consultation with the patient's primary care provider or neurologist to provide consistent disease management.
- Intravenous methylprednisolone effectively promotes earlier resolution of recurrences.
- Intravenous methylprednisolone has been shown to speed the recovery from vision loss from optic neuritis.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.