CHAPTER 21

# Brainstem and Multiple Cranial Nerve Syndromes

The brainstem is a compact structure, with cranial nerve (CN) nuclei, nerve fascicles, and long ascending and descending tracts all closely juxtaposed. Structures and centers in the reticular formation control many vital functions. Brainstem diseases are serious and often life threatening. Involvement of the intricate network of neural structures often causes a plethora of clinical findings. Brainstem syndromes typically involve dysfunction of one or more CNs. Deficits due to dysfunction of individual nerves are covered in the preceding chapters. This chapter discusses conditions that cause dysfunction beyond the distribution of a single CN, involving more than one CN, or conditions that involve brainstem structures in addition to the CN nucleus or fascicles. The first part covers intramedullary disorders of the brainstem, and the second part covers disorders that involve multiple CNs in their extramedullary course.

Some may argue it is sufficient to recognize that a brainstem disorder exists and to define the process more precisely with an imaging study. However, some important clinical conditions may cause major brainstem dysfunction without dramatically changing the appearance of the imaging study. Examples of processes easily missed radiographically include Wernicke's disease, progressive bulbar palsy (PBP), progressive supranuclear palsy, basilar artery migraine, Whipple's disease, syringobulbia, olivopontocerebellar atrophy, and Gerstmann-Sträussler-Scheinker syndrome. With disorders causing multiple CN deficits, the imaging studies are often not helpful.

## BRAINSTEM SYNDROMES

In the brainstem, descending motor tracts prior to decussation, as well as

ascending sensory pathways that have already crossed, lie in intimate relation to the lower motor neurons of the CN nuclei. With a few exceptions, CNs innervate structures of the head and neck ipsilaterally. A process affecting the brainstem long tracts on one side causes clinical abnormalities on the opposite side of the body. For this reason, focal brainstem lesions are characterized by “crossed” syndromes of ipsilateral CN dysfunction and contralateral long motor or sensory tract dysfunction. For instance, in the right side of the pons, the nuclei for CNs VI and VII lie in proximity to the right corticospinal tract, which is destined to decussate in the medulla to innervate the left side of the body. The patient with a lesion in the right pons will have CN findings on the right, such as a sixth or seventh nerve palsy, and a hemiparesis on the left.

This crossed deficit will often be associated with symptoms reflecting dysfunction of other brainstem structures or their connections. Because of the rich vestibular and cerebellar connections, patients with brainstem disease often have dizziness or vertigo, unsteadiness, imbalance, incoordination, difficulty walking, nausea, and vomiting. Pharyngeal and laryngeal muscles are innervated by neurons in the brainstem, and patients often have dysarthria or dysphagia. Dysfunction of CNs III, IV, and VI or their connections may cause ocular motility abnormalities. Unless the process has impaired the reticular activating system, these patients are normal mentally—awake, alert, able to converse (though perhaps dysarthric), not demented, not confused, and not aphasic. The fourth ventricle and cerebral aqueduct lie nearby; if these are involved, patients may develop obstructive hydrocephalus. Although most pathologic processes that involve the brainstem occur in other parts of the brain, some disorders are characterized by primarily brainstem involvement (e.g., central pontine myelinolysis, medulloblastoma, and olivopontocerebellar atrophy). With vascular lesions, the clinical deficit depends on whether the occlusive process has involved the paramedian perforating, short circumferential, or long circumferential branches of the basilar artery.

From an anatomical standpoint, brainstem syndromes may be localized by considering the rostral to caudal level and the medial to lateral level. The rostral to caudal localization is determined by the CN involvement. Abnormality of CN III or IV, or a vertical gaze abnormality, indicates a midbrain lesion; CN VI or VII, or a horizontal gaze palsy—a pontine lesion; CN VIII—a pontomedullary junction lesion; and CNs IX, X, XI, or XII—a medullary lesion. Because of the vast longitudinal extent of the spinal tract of CN V, facial sensory abnormalities can occur with lesions anywhere from the pons to the cervical spinal cord.

The long motor tracts tend to lie medial, and the long sensory tracts lateral, in the brainstem. Somatic motor nuclei (extraocular and hypoglossal) are paramedian; branchiomotor nuclei are more lateral. Involvement of descending motor tracts or somatic motor nuclei indicates medial lesions; involvement of long sensory tracts, branchiomotor nuclei, and special sensory nuclei indicates lateral lesions. The cerebellar peduncles also lie laterally. The alar plate–derived sensory nuclei lie laterally and are separated from the basal plate–derived motor nuclei by the sulcus limitans (Figures 11.2 and 11.4). Paramedian perforators from the basilar artery perfuse the midline structures; circumferential arteries perfuse the lateral structures. There are therefore medial and lateral medullary syndromes; medial and lateral inferior, middle, and superior pontine syndromes; and the midbrain syndromes. The posterior inferior cerebellar artery (PICA) supplies the lateral medulla; the anterior inferior cerebellar artery (AICA) supplies the inferior lateral pons; and the superior cerebellar artery (SCA) supplies the superior lateral pons. Paramedian lesions are typically lacunar; lateral lesions are more often from disease of the larger circumferential vessels. The lateral medullary and pontine syndromes are often referred to by their vascular territory designations: PICA, AICA, and SCA.

Occlusion of medial pontine branches of the basilar artery may cause involvement of the nuclei of CNs VI and VII or their emerging fibers, the medial longitudinal fasciculus (MLF), the corticospinal tract, the medial lemniscus, and the pontine paramedian reticular formation. Clinical manifestations may include ipsilateral facial nerve palsy, abducens palsy, horizontal gaze palsy, internuclear ophthalmoplegia (INO), or impaired taste, with contralateral corticospinal weakness and impaired lemniscal sensation. Thrombosis of the lateral pontine branches of the basilar artery produces ischemia that may involve the middle and superior cerebellar peduncles, the vestibular and cochlear nuclei, the facial and trigeminal motor nuclei, the trigeminal sensory nucleus, and the spinothalamic tract. Findings may include ipsilateral cerebellar ataxia and dysfunction of CNs V, VII, and VIII, with contralateral loss of pain and temperature sensation on the trunk and extremities. Occlusion of the internal auditory artery causes unilateral deafness and impaired vestibular function.

## CLASSICAL BRAINSTEM SYNDROMES

Many of the early neurologic pioneer clinicians described the clinical findings

due to a focal process affecting the brainstem. These physicians practiced in an era when disorders such as tuberculoma, syphilitic gumma, and tumor were seen much more often than today. Many of the classical brainstem syndromes as originally described were not due to ischemia, and the effects of tuberculoma, gumma, and similar lesions are not limited to vascular distributions. Some degree of mismatch has therefore resulted between the classic descriptions and the current environment when most brainstem syndromes are due to ischemia. There has also been significant drift of many of the eponymic syndromes through failure to honor precisely the original descriptions. Liu et al. pointed out the variability in textbook descriptions of Claude's, Benedikt's, and Nothnagel's syndromes and noted the difference in textbook descriptions compared to the original papers. Box 21.1 contains a discussion of the classical eponymic brainstem syndromes, largely from a historical perspective, and Table 21.1 summarizes the clinical features.

Wallenberg described the lateral medullary syndrome (LMS), the most common form of brainstem stroke. Wallenberg's original patient had an occlusion of the PICA, but LMS is most often due to ischemia in the PICA distribution because of vertebral artery occlusion (Figure 21.1). Typical manifestations include vertigo, nausea and vomiting, nystagmus, hoarseness, dysphagia, dysphonia, singultus, ipsilateral hemiataxia, and numbness of the ipsilateral face and contralateral body. Occipital headache or pain in the back of the neck may occur at the onset; prominent pain raises the possibility of vertebral artery dissection. The patient may be unable to talk and swallow initially. Clinical findings are summarized in Table 21.1.

## BOX 21.1

### Classical Brainstem Syndromes

**Midbrain Syndromes**

Weber described a patient with a hematoma of one cerebral peduncle, which damaged the corticospinal and corticobulbar tracts and the exiting third nerve. The patient had a contralateral hemiparesis involving face, arm, and leg and an ipsilateral complete third nerve palsy. Benedikt described one patient with a similar peduncular lesion due to a midbrain tuberculoma, which extended further into the tegmentum and involved the regions of the substantia nigra and red nucleus, causing tremor and involuntary movements

of the hemiparetic limbs. Two clinically similar patients were not studied pathologically; one probably had meningovascular syphilis. Claude described a patient with a midbrain infarction in whom the corticospinal pathways were not involved; the clinical picture was ipsilateral third nerve palsy and contralateral cerebellar ataxia due to involvement of the superior cerebellar peduncle. Debate remains about how much red nucleus involvement occurs in Claude's and Benedikt's syndrome. Seo concluded on the basis of clinical and magnetic resonance imaging (MRI) studies that the lesion usually lies just caudal and medial to the red nucleus and that the tremor and ataxia are due to involvement of the cerebellar outflow pathways in the superior cerebellar peduncle.

These three midbrain syndromes are variations on a theme. The lesion is anterior—in the cerebral peduncle—in Weber's syndrome, causing hemiparesis. It is more posterior—in the tegmentum—in Claude's syndrome, causing hemiataxia. In Benedikt's syndrome, the lesion is more extensive, involving both the tegmentum and the peduncle, causing hemiparesis with tremor and ataxia of the involved limbs; Benedikt's is essentially Weber's + Claude's. Because the fascicles of cranial nerve (CN) III are scattered in their course through the midbrain, the third nerve palsy in any of these syndromes may be partial.

Nothnagel's (ophthalmoplegia-ataxia) syndrome is different; it is more a variant of Parinaud's syndrome, with unilateral or bilateral third nerve palsy and ataxia accompanied by vertical gaze deficits and other neurologic signs. The lesion affects the midbrain tectum and is often neoplastic. Nothnagel's original patient had a pineal sarcoma.

**Pontine Syndromes**

Millard and Gubler separately described patients with an ipsilateral lower motor neuron facial nerve palsy and contralateral hemiparesis due to a lesion involving the pons. Gubler's cases included three with a tumor, one with a stroke, and one with a brownish softening. Millard reported one case due to pontine hemorrhage as a letter to the editor in the journal where Gubler reported his cases. In all cases, the lesion lay in the lateral pons and did not involve CN VI; the patients had no ocular motility disturbance. Nevertheless, it is common to see sixth nerve palsy included in textbook descriptions of Millard-Gubler syndrome. Gubler was a senior clinician reporting several cases; Millard had just graduated from medical school, was essentially a resident, and reported only one. Gubler instructed the journal editor to give

Millard precedence, hence the eponym.

Foville described a patient with an ipsilateral lower motor neuron facial palsy and a horizontal gaze palsy, with a contralateral hemiparesis; there was no pathology but the onset was apoplectic. Landry, in a letter commenting on Foville's case, described a patient with sixth nerve palsy and contralateral hemiplegia, including the face, due to pontine ischemia in a patient with syphilis. Yelloly had described a case of abducens palsy with contralateral hemiplegia 50 years previously. Raymond described a patient with sixth nerve palsy and contralateral hemiplegia, but it is not clear that the hemiplegia was of pontine origin.

**Medullary Syndromes**

There are two primary medullary syndromes, the lateral (Wallenberg) and the medial (Dejerine). The rare medial medullary syndrome is summarized in Table 21.1. In a study of clinical magnetic resonance imaging (MRI) correlation in medial medullary infarction, classical Dejerine's syndrome (ipsilateral tongue weakness with contralateral hemiparesis and lemniscal sensory loss) was seen in 64% of patients; the remainder had partial lesions, which may be less readily recognized. In a series of 18 patients, the most common manifestation of medial medullary stroke was a unilateral sensorimotor deficit. The extremely rare bilateral medial medullary syndrome causes quadriparesis and other abnormalities. Isolated tongue weakness has been reported because of bilateral medullary infarction. Other syndromes of the medulla (Avellis's, Jackson's, Schmidt's, Céstan-Chenais, and Babinski-Nageotte) are described in Table 21.1. Except for the occasional upper motor neuron facial palsy in Wallenberg's syndrome, there is sparing of facial motor function in all of the medullary syndromes.

In a series of MRI-verified LMS, the most common findings were ipsilateral Horner's syndrome and ataxia and contralateral body hypalgesia. The spontaneous nystagmus is usually horizontal or mixed horizontal-torsional. Horizontal nystagmus beats away from the side of the lesion and may be second or third degree. Torsional nystagmus with the upper poles beating away from the side of the lesion is also common. The nystagmus is influenced by head and eye position and by fixation. Dysphagia is common. It is often more severe than would be expected simply from a lesion of the nucleus ambiguus, and disruption of connections to a premotor swallowing center in the dorsolateral medulla has

been postulated. Partial resolution and survival is the rule; the ability to swallow and talk returns, although residual hoarseness, persistent ataxia, and sensory changes may remain. Aspiration is a major threat. The presence of dysphonia, soft palate dysfunction, or facial sensory loss suggests an increased risk. Although LMS is usually ischemic, it has also been described with aneurysm, abscess, hematoma, arteriovenous malformation, demyelinating disease, and metastatic neoplasm. The LMS may have many unusual manifestations (Box 21.2).

## ANATOMIC BRAINSTEM SYNDROMES

The other approach to organizing brainstem syndromes is by the anatomical area or the major blood vessel involved. The midbrain syndromes are variations and combinations of an ipsilateral third nerve palsy and weakness, ataxia, or tremor of the contralateral limbs; this is due to ischemia in the distribution of paramedian penetrating vessels from the rostral basilar artery. The LMS is discussed in the previous section, and the medial medullary syndrome is discussed in Box 21.1.

The vascular pontine syndromes can be divided into medial and lateral and into superior, middle, and inferior. The medial pontine syndromes are due to disease of the paramedian perforators; the lateral pontine syndromes are due to disease of the circumferential arteries. The AICA supplies the lateral inferior pons and upper medulla, whereas the SCA supplies the lateral upper pons. The midpons is supplied by a short circumferential artery. Just as PICA ischemia causes the LMS, ischemia in the AICA distribution causes the lateral inferior pontine syndrome; and ischemia in the SCA distribution causes the lateral superior pontine syndrome. The generally recognized pontine syndromes are therefore the medial inferior pontine, lateral inferior pontine (AICA), medial and lateral midpontine, medial superior pontine, and lateral superior pontine (SCA). The vascular pontine syndromes are summarized in Table 21.2. In a series of patients with lesions involving the AICA distribution, only 29% had the complete AICA syndrome. Partial syndromes were characteristic of small vessel disease; more widespread involvement indicated basilar artery occlusive disease. The SCA syndrome is also often partial. Basilar branch occlusion may involve any of the branches of the basilar artery. The mechanism is atherothrombotic occlusion at the point of origin of the branch, and the infarction typically extends

to the ventral surface of the pons.

Vertebrobasilar transient ischemic attacks (vertebrobasilar insufficiency, VBI) are episodes of brainstem ischemia due to occlusive disease involving the posterior circulation. Symptoms depend upon which region of the brainstem is ischemic. The clinical manifestations of an attack of VBI are typically bilateral, with varying degrees of weakness, numbness, and CN dysfunction. Accompanying symptoms indicative of brainstem dysfunction include diplopia, dysarthria, dysphagia, vertigo, nausea, and vomiting. There may be impaired vision due to ischemia in the posterior cerebral artery distribution. Bilateral sensory complaints are common, especially circumoral paresthesias. Attacks usually last from a few minutes to half an hour, sometimes longer.

**TABLE 21.1 Summary of the Classical Named Brainstem Syndromes**

| Syndrome | Lesion Location | Structures Involved | Clinical Findings | Comment |
|---|---|---|---|---|
| Parinaud's | Midbrain dorsum | Quadrigeminal plate region; pretectum; periaqueductal gray matter | Impaired upgaze; convergence retraction nystagmus; dilated pupils with light near dissociation | Usually due to mass lesion in the region of the posterior third ventricle, most often pinealoma, or due to midbrain infarction |
| Weber's | Midbrain base | CN III fibers; cerebral peduncle | Ipsilateral CN III palsy; contralateral hemiparesis | Usually vascular |
| Benedikt's | Midbrain tegmentum | CN III fibers; red nucleus; CST | Ipsilateral CN III palsy; contralateral hemiparesis with ataxia, hyperkinesia, and tremor ("rubral tremor") | Usually vascular |
| Claude's | Midbrain tegmentum | CN III fibers; red nucleus; SCP | Ipsilateral CN III palsy; contralateral ataxia and tremor ("rubral tremor") | Usually vascular |
| Nothnagel's | Midbrain tectum | Ipsilateral or bilateral CN III | Oculomotor palsies; ataxia | Usually neoplastic |
| Millard-Gubler | Pons | CN VII; CST | Ipsilateral peripheral facial palsy; contralateral hemiparesis | Usually vascular; CN VI not involved; usage is inconsistent |
| Foville's (Raymond-Foville) | Pons | CN VII; lateral gaze center, CST | Ipsilateral facial palsy and horizontal gaze palsy; contralateral hemiparesis | Usually vascular; usage is inconsistent |
| Raymond's (Yelloly, Landry) | Pons | CN VI; CST | Ipsilateral abducens palsy; contralateral hemiparesis | Usually vascular, often lumped with Foville's syndrome; usage is inconsistent |
| Wallenberg's (lateral medullary syndrome) | Lateral medullary tegmentum | Spinal tract of CN V and its nucleus; nucleus ambiguus; emerging fibers of CNs IX and X; LST; descending sympathetic fibers; vestibular nuclei; inferior cerebellar peduncle; afferent spinocerebellar tracts; lateral cuneate nucleus | Loss of pain and temperature of ipsilateral face and contralateral body; decreased ipsilateral corneal reflex; weakness of ipsilateral soft palate; loss of ipsilateral gag reflex; paralysis of ipsilateral vocal cord; ipsilateral central Horner's syndrome; nystagmus; cerebellar ataxia of ipsilateral limbs; lateropulsion | Several variants recognized; occasional ipsilateral upper motor neuron facial palsy due to involvement of aberrant CST; facial sensation sometimes preserved; ischemia in PICA distribution but more often due to vertebral artery occlusion |
| Avellis' syndrome | Medullary tegmentum | CN X; LST; nucleus ambiguus | Ipsilateral palatal and vocal cord weakness; loss of pain and temperature of contralateral body | Usually due to vertebral artery thrombosis; occasional involvement of ML and ST with loss of touch and proprioception of contralateral body; occasional ipsilateral Horner's syndrome occasional contralateral hemiparesis |
| Jackson's syndrome | Medullary tegmentum | CN X fibers or nucleus ambiguus; CNs XI and XII | Ipsilateral flaccid paralysis of the soft palate, pharynx, and larynx; flaccid weakness and atrophy of SCM and trapezius (partial) and of the tongue | Also known as vago-accessory-hypoglossal paralysis; more likely due to extramedullary multiple cranial nerve palsy |
| Schmidt's | Lower medullary tegmentum | Nucleus ambiguus; bulbar and spinal nuclei of CN XI and/or their radicular fibers | Ipsilateral paralysis of soft palate, pharynx, and larynx; flaccid weakness and atrophy of SCM and trapezius (partial) | Also known as vago-accessory syndrome; more likely due to extramedullary multiple cranial nerve palsy |

*(continued)*

| | | | | |
|---|---|---|---|---|
| Céstan-Chenais | Medullary tegmentum | Nucleus ambiguus; ICP; sympathetics; CST; ML | Ipsilateral weakness of soft palate, pharynx, and larynx; cerebellar ataxia; Horner's syndrome; contralateral hemiparesis with loss of posterior column function | Due to vertebral artery occlusion below the origin of the PICA; differs from Wallenberg's because of CST and ML involvement and absence of changes in pain and temperature |
| Babinski-Nageotte (hemimedullary syndrome) | Medial and lateral medulla | Nucleus ambiguus; solitary tract; spinal tract of V; ICP; sympathetics; CST; ML; +/–XII | Ipsilateral paralysis of soft palate, pharynx, larynx, +/– tongue; loss of taste on posterior third of tongue; impaired facial pain and temperature; ataxia; Horner's syndrome; contralateral hemiparesis; impaired posterior column function; +/– impaired pain and temperature | Caused by multiple or scattered lesions, chiefly in the distribution of the vertebral artery; similar to, perhaps the same as, Céstan-Chenais |
| Medial medullary syndrome (Dejerine's anterior bulbar syndrome, pyramidhypoglossal syndrome, alternating hypoglossal hemiplegia) | Medial medulla | XII nucleus or fibers; medullary pyramid (at/near decussation); +/–ML | Ipsilateral tongue weakness; contralateral hemiparesis (sparing the face); +/– impairment of posterior column function; LST functions spared | Due to ischemia in the distribution of paramedian perforator or the anterior spinal artery, findings may be bilateral and of variable laterality because of involvement of the pyramidal decussation and variations in the anatomy of the anterior spinal artery |

CN, cranial nerve; CST, corticospinal tract; ICP, inferior cerebellar peduncle; LST, lateral spinothalamic tract; ML, medial lemniscus; PICA, posterior inferior cerebellar artery; SCM, sternocleidomastoid; SCP, superior cerebellar peduncle; ST, solitary tract.

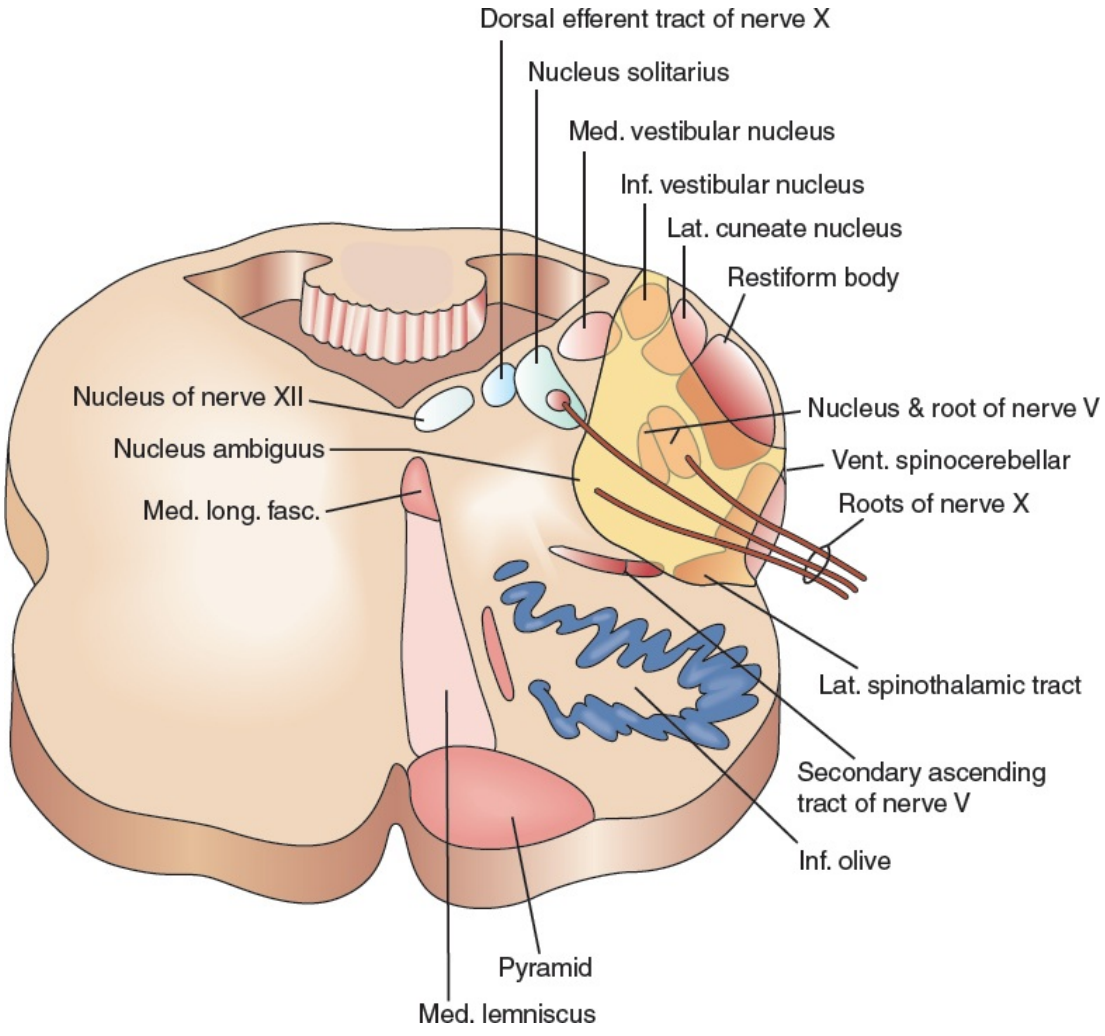


**FIGURE 21.1** Cross section of the medulla illustrating the lesion in the lateral medullary syndrome.

Basilar artery occlusion may have a gradual onset or a fluctuating course with prodromata, but often, the symptoms appear apocalyptically; death may occur

within a short period of time. When the onset is acute, there is sudden loss of consciousness with gradually increasing coma and flaccid extremities or decerebrate rigidity. The onset may be subacute with prodromal vertigo, nausea, headache, and paresthesias, which may occur up to 2 weeks before the stroke, followed by bilateral CN and long tract abnormalities (progressive basilar thrombosis). Fisher described a "herald hemiparesis" in basilar artery thrombosis, frequently present at an early stage, when brainstem signs are absent or inconspicuous, followed within a few hours by bilateral hemiplegia and coma or a locked-in state (Chapter 51). With total occlusion, there is either hemiplegia on one side and partial hemiplegia on the other, or quadriplegia. Involvement of ascending sensory pathways causes a disturbance of both deep and superficial sensations on the body, the extremities, and sometimes the face. The pupils are usually miotic and poorly reactive. Ocular bobbing and palatal myoclonus may occur. The neurologic signs are characteristically variable and complex. Coma and decerebrate rigidity with respiratory and circulatory instability are common.

Patients with coma at the outset have a grave prognosis. The site of occlusion is usually in the lower third of the basilar artery. The outcome with severe brainstem ischemic disease is usually poor. Death is a common outcome of complete basilar artery occlusion. Patients may be left in a locked-in state (Chapter 51).

## BOX 21.2

### Unusual Manifestations of Lateral Medullary Syndrome

Patients may have an ipsilateral upper motor neuron facial palsy due to involvement of Dejerine's aberrant pyramidal tract (see facial nerve chapter). In the series of Sacco et al., mild ipsilateral facial weakness was present in 42% of patients, usually limited to the lower face. The hypalgesia may involve only the ipsilateral face or only the contralateral body; the classical crossed pattern occurs only in a minority. Other patterns of sensory loss are discussed in Chapter 15. Ocular motor abnormalities are common, including skew deviation with ipsilateral hypotropia, ocular tilt reaction, bizarre environmental tilt illusions including world inversion (floor on ceiling phenomenon), ipsilateral gaze deviation with impaired contralateral pursuit, saccadic abnormalities, seesaw nystagmus, and eyelid nystagmus. Ocular abnormalities and facial weakness are common and do not imply extension

of the lesion beyond the lateral medulla. There may be contralateral hemiparesis due to inferior extension of the zone of ischemia to the medullary pyramid prior to decussation or ipsilateral hemiparesis due to inferior extension to the lateral funiculus of the rostral spinal cord (Opalski's submedullary syndrome, Figure 21.2). Rarely, there is impaired sensation of the ipsilateral arm and leg due to inferior extension to the gracile and cuneate nuclei, ipsilateral loss of taste, or contralateral facial hypalgesia. Other unusual manifestations include wild unilateral, proximal arm ataxia; neurotrophic ulceration of the face; inability to sneeze; paroxysmal sneezing; loss of taste; Ondine's curse; and weakness of the sternocleidomastoid. Chronic central facial pain develops in some patients.

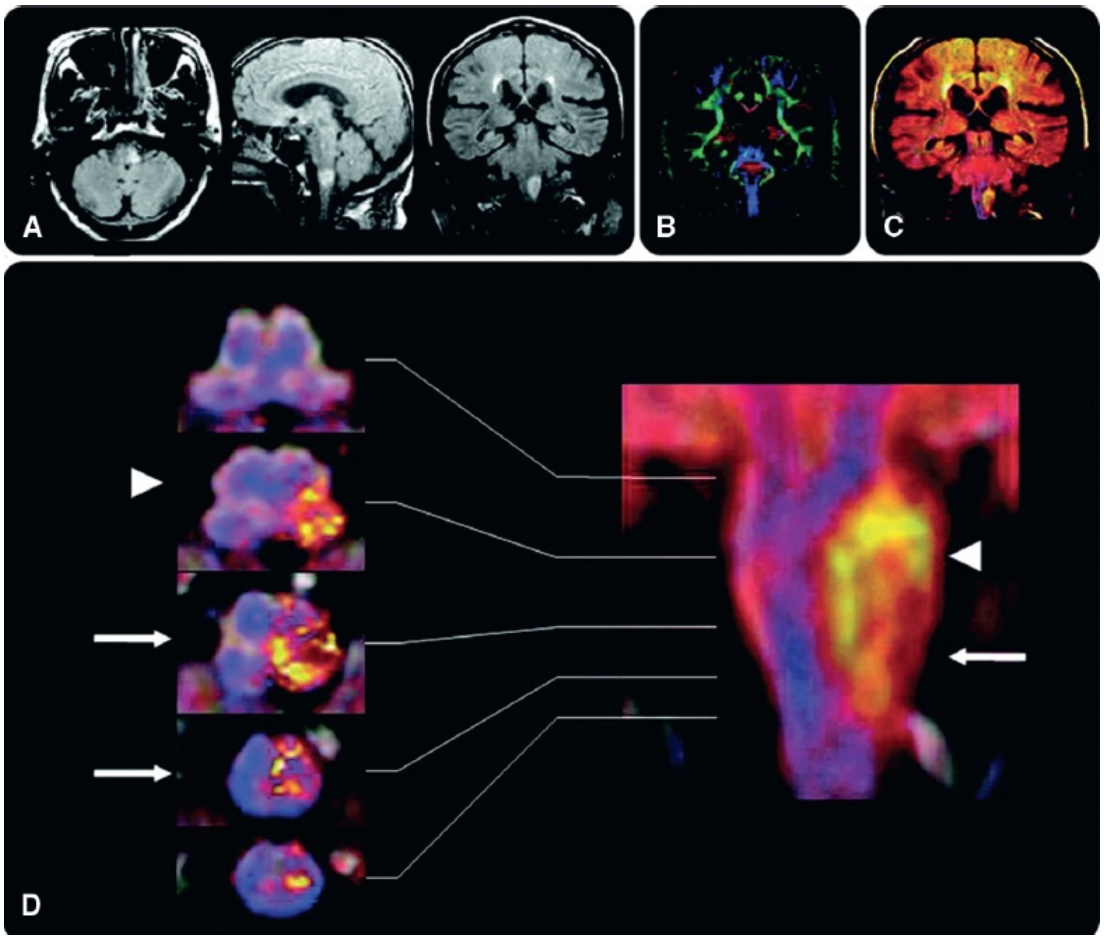


**FIGURE 21.2** Imaging features of Opalski syndrome. Fluid-attenuated inversion recovery MRI. **A.** Directionally encoded map with hues reflecting tensor orientation. **B.** Superimposed images. **C,D.** A *yellow halo* represents the infarct and *blue lines* represent the pyramidal tracts (coronal); the tracts fuse at the decussation (transverse). Caudal extension of the lesion involves the ipsilateral corticospinal tract (*arrows*) after the decussation (*arrowheads*). (Reprinted from Nakamura S, Kitami M,

Furukawa Y. Opalski syndrome: ipsilateral hemiplegia due to a lateral-medullary infarction. *Neurology* 2010;75[18]:1658, with permission.)

**TABLE 21.2 Summary of the Vascular Pontine Syndromes Organized by Anatomical Region and Blood Vessel Involved**

| Syndrome | Structures Involved | Clinical Findings | Comment |
|---|---|---|---|
| Medial inferior pontine | PRRF; CN VI nucleus or fibers; MCP; CST; ML | Ipsilateral CN VI or horizontal gaze palsy; ataxia. Paresis and impaired lemniscal sensation of contralateral limbs | Due to occlusion of paramedian perforating vessel |
| Lateral inferior pontine (AICA syndrome) | CN VII nucleus or fibers; CN VIII nuclei; MCP; ICP; CST; principal and spinal nucleus of CN V; LST; ST; flocculus and inferior surface of cerebellar hemisphere | Ipsilateral cerebellar ataxia; loss of pain and temperature sensation and diminished light touch sensation of face; impaired taste sensation; central Horner's syndrome; deafness; peripheral type of facial palsy. Loss of pain and temperature sensation of contralateral limbs | Due to occlusion of AICA |
| Medial midpontine | MCP; CST; ML | Ipsilateral ataxia. Contralateral weakness of arm, leg, and face; gaze deviation; +/– impaired lemniscal sensation | Due to occlusion of paramedian perforating vessel |
| Lateral midpontine | MCP; CN V motor and sensory nuclei or fibers | Ipsilateral ataxia; weakness of muscles of mastication; impaired facial sensation | Due to occlusion of short circumferential artery |
| Medial superior pontine | SCP and/or MCP; MLF, CTT; CST; ML | Ipsilateral ataxia; INO. Contralateral weakness of arm, leg, and face; +/– impaired lemniscal sensation. Palatal myoclonus | Due to occlusion of paramedian perforating vessel |
| Lateral superior pontine (SCA syndrome, Mills' syndrome) | SCP and MCP; LST; lateral part of ML; superior cerebellar hemisphere | Ipsilateral ataxia; Horner's syndrome; skew deviation. Contralateral impairment of pain, temperature, and lemniscal sensation. Vertigo; dysarthria; lateropulsion to side of lesion | Due to occlusion of superior cerebellar or distal basilar artery |

AICA, anterior inferior cerebellar artery; CN, cranial nerve; CST, corticospinal tract; CTT, central tegmental tract; ICP, inferior cerebellar peduncle; INO, internuclear ophthalmoplegia; LST, lateral spinothalamic tract; MCP, middle cerebellar peduncle; ML, medial lemniscus; MLF, medial longitudinal fasciculus; PRRF, pontine paramedian reticular formation; SCA, superior cerebellar artery; SCP, superior cerebellar peduncle; ST, solitary tract.

The "top of the basilar" syndrome is caused by ischemia in the distribution of the distal basilar artery, usually embolic, involving the rostral brainstem, thalamus, and portions of the cerebral hemispheres fed by the posterior cerebral arteries. A variety of oculomotor and pupillary abnormalities may occur, along with visual and behavioral abnormalities, often without significant extremity weakness.

Patients with pontine hemorrhage have a clinical picture similar to basilar artery occlusion, but warning symptoms are less apt to occur. They are comatose and quadriplegic and have bilateral facial paralysis, bilateral horizontal gaze palsies, and pinpoint poorly reactive pupils. Hyperthermia is common. Imaging studies often show a large hematoma in the midpons. Few patients survive such an event. The initial level of consciousness and the size of the hematoma are strongly related to the outcome.

Pressure on the brainstem due to supratentorial mass effect can cause either

lateral transtentorial herniation (uncal syndrome), with third nerve involvement and signs of lateral midbrain compression, or central transtentorial herniation, with constricted pupils, Cheyne-Stokes respirations, bilateral corticospinal tract signs, decorticate rigidity, and progressive impairment of diencephalic, midbrain, pontine, and medullary function. Because of the patterns of venous drainage, increased intracranial pressure and herniation at either the foramen magnum or the tentorium may cause secondary bleeding into the midbrain, pons, or medulla. Duret hemorrhages are secondary hemorrhages into the upper brainstem that occur with increased intracranial pressure and descending transtentorial herniation. Brainstem hemorrhage may cause hyperthermia, respiratory abnormalities, coma, and finally death in patients with brain tumors, subarachnoid hemorrhage, cerebral hemorrhage, trauma, rapidly expanding supratentorial mass lesions, or similar conditions causing an increase in intracranial pressure. Affected patients rarely survive; Stiver et al. reported an exception in a young adult traumatic brain injury patient.

When increased intracranial pressure causes tonsillar herniation, the cerebellar tonsils and lower medulla are forced downward through the foramen magnum. Although tonsillar herniation is a feared complication of lumbar puncture done in the face of increased intracranial pressure, it is in fact rare. Medullary compression causes profound impairment of all vital functions, with bradycardia, either a fall or rise in blood pressure, slow or rapid respirations, soaring temperature, convulsions, unconsciousness, and death. The Cushing (vasopressor) reflex (response, reaction, or effect) is hypertension, increased pulse pressure, bradycardia, and slow, irregular respirations seen in patients with increased intracranial pressure and brainstem compression. The full triad occurs in only about one-third of cases, and some patients may have isolated hypertension. On postmortem examination, a pressure cone may be seen on the medulla.

## BOX 21.3

### Other Brainstem Syndromes

The one-and-a-half syndrome is a horizontal gaze palsy and ipsilateral internuclear ophthalmoplegia, or INO (Chapter 14). The association of an ipsilateral lower motor neuron facial nerve palsy and a one-and-a-half syndrome has been termed the eight-and-a-half syndrome. The Brissaud-

Sicard syndrome is ipsilateral hemifacial spasm and contralateral hemiparesis due to a pontine lesion. The lateral pontomedullary syndrome consists of the findings of the lateral medullary syndrome with additional involvement of CNs VII and VIII consistent with extension of the lesion to the inferior pons. Raymond-Cestan syndrome is horizontal or vertical gaze palsy, contralateral hemiparesis or quadriparesis, hemianesthesia, and athetosis due to basilar branch occlusion. Rasdolsky's syndrome is contracture and paresis of the masseter and facial muscles due to neoplasm of ipsilateral pontine tegmentum. Marie-Foix syndrome is contralateral hemiparesis and hypalgesia with ipsilateral cerebellar ataxia due to a lesion involving the lateral pons. Other unusual manifestations of brainstem disease include pontine anosognosia, cognitive dysfunction, painful isolated Horner's syndrome, head shaking nystagmus, jaw opening dystonia, hemidystonia, facial pain syndromes, a sensory level on the trunk, unilateral hyper- or hypohidrosis, upside-down reversal of vision, tonic seizures, and convulsive-like movements.

Aneurysms of the basilar or vertebral arteries or their branches, and hemangiomas, may cause extramedullary compression and CN involvement. Arteriovenous malformations may cause intramedullary or extramedullary dysfunction, depending on their extent and location. Extravasation of blood about the base of the brain from subarachnoid or intracerebral hemorrhage may affect the CNs as they leave the skull.

Lacunes are small, deep infarctions in the territory of a deep penetrating arteriole. Hypertension is the major predisposing factor. The brainstem, particularly the pons, is a common location for lacunar infarction. Brainstem lacunar syndromes include pure motor stroke, dysarthria–clumsy hand syndrome, and ataxic hemiparesis (homolateral ataxia and crural paresis). Pure motor stroke is the most common lacunar syndrome. Although lacunar syndromes, especially pure sensory stroke and ataxic hemiparesis, are highly predictive of lacunar infarction, in about one in four patients the etiology involves a nonlacunar mechanism.

Other unusual, typically vascular, brainstem syndromes are briefly described in Box 21.3.

## Nonvascular Brainstem Disorders

Brainstem gliomas are astrocytomas that diffusely infiltrate the brainstem. Most involve the pons, but they may affect any level of the brainstem, typically causing a combination of multiple cranial nerve palsies (MCNPs), gaze palsy, long tract signs, and ataxia. Because of the slow evolution, there is sometimes a paucity of neurologic signs in spite of the size of the tumor. Ventricular obstruction may produce hydrocephalus and increased intracranial pressure. Ependymomas and medulloblastomas may also involve the brainstem. Extramedullary tumors (neurofibromas, schwannomas, meningiomas, hemangiomas, metastases) may cause pressure effects. The course of a brainstem neoplasm is progressive. Increased intracranial pressure may appear late, particularly in brainstem gliomas. Extrinsic metastases and neoplasms that spread by direct extension from the nasopharynx and neighboring sites may cause widespread CN involvement and bone erosion with signs of brainstem compression. Tuberculomas, sarcoidosis, and other granulomas may produce a picture similar to neoplasms.

Brainstem encephalitis (Bickerstaff's encephalitis) is a clinical syndrome of acute diffuse or multifocal brainstem dysfunction with cerebrospinal fluid (CSF) pleocytosis and increased protein. Actual viral infection has seldom, if ever, been documented, and the disease is usually immunologically mediated. Patients develop ophthalmoplegia and ataxia followed by gradual brainstem dysfunction and altered consciousness. The illness is usually preceded by a viral infection. Some patients have serum anti-GQ1b IgG autoantibodies, the same antibody found in Miller Fisher syndrome (ophthalmoplegia, ataxia, and areflexia). Bickerstaff's brainstem encephalitis is not to be confused with Bickerstaff's (basilar artery) migraine (see below). Brainstem encephalitis may be paraneoplastic. Rhombencephalitis refers to inflammatory disease affecting the hindbrain (brainstem and cerebellum). It has a wide variety of etiologies, including multiple sclerosis (MS), Behcet's disease, paraneoplastic syndrome, lupus, and viral and tuberculous infection. Listeria monocytogenes is particularly likely to cause rhombencephalitis; it accounted for 9% of cases in one series.

Demyelinating disease frequently involves the brainstem. INO due to a demyelinating lesion involving the MLF is a very common clinical manifestation of MS. MS can cause lesions elsewhere in the brainstem and can occasionally simulate one of the vascular syndromes. Acute disseminated encephalomyelitis may affect the brainstem, and the involvement is occasionally limited to the brainstem.

In central pontine myelinolysis (osmotic demyelination syndrome), there is

widespread, symmetric myelin loss in the central portion of the pons. Lesions commonly occur in other sites as well (extrapontine myelinolysis). Central pontine myelinolysis occurs especially in alcoholics or other malnourished or debilitated individuals and after correction of severe hyponatremia. It typically begins with diplopia, dysphagia, dysarthria, and other evidence of brainstem dysfunction, followed by quadriplegia, mutism, and extensor rigidity. Central pontine myelinolysis runs a fulminating course and is often fatal.

Developmental or congenital anomalies of the craniocervical junction are frequently associated with brainstem dysfunction. The bony walls of the foramen magnum and upper spinal canal lie in close anatomic relationship to the lower brainstem, upper spinal cord, and cerebellum. Neurologic abnormalities may be produced by mechanical compression by the bony abnormality, but often the bony abnormality and the neural abnormality are part of the same process. Platybasia, basilar impression, occipitalization of the atlas, and cervical spina bifida are examples of primary bony abnormalities. Klippel-Feil syndrome is the congenital fusion of two or more cervical vertebrae. There may be accompanying craniocervical junction abnormalities. The associated neurologic abnormalities may include myelopathy, radiculopathy, syringomyelia, and mirror movements.

Arnold-Chiari (or simply Chiari, who made the greater contribution) malformation is a congenital maldevelopment of the brainstem and cerebellum. The cerebellar tonsils are herniated or displaced down into the upper cervical spinal canal. With more severe maldevelopment, the inferior vermis, lower medulla, and fourth ventricle may also be displaced below the foramen magnum. Clinical manifestations include headache, cerebellar ataxia, nystagmus (typically downbeat), and other brainstem deficits. Three varieties commonly occur. Type 1 is the hindbrain malformation only; it can present in adulthood. Mild type 1 Chiari malformations are not uncommonly found on MRI imaging done for other reasons and may be totally asymptomatic. Type 2 is a more severe hindbrain defect usually associated with a lumbar meningomyelocele. Type 3 is the same as type 2 except that the meningomyelocele or encephalocele occurs in the occipitocervical region. The Dandy-Walker syndrome is agenesis of the cerebellar vermis with a massively dilated fourth ventricle forming a cystic structure that occupies most of the posterior fossa.

Syringobulbia is a slit-like cavity in the brainstem. A brainstem syrinx is usually a rostral extension of a syringomyelic cavity from the cervical spinal cord in a patient with a Chiari malformation, but syringobulbia may rarely occur

de novo. In syringobulbia, the syrinx most often involves the lateral medullary tegmentum. The cavity is usually restricted to the lower brainstem but may extend to the pons and rarely higher. The cavity and the resultant clinical picture are typically asymmetric, with lower CN dysfunction, facial numbness, and nystagmus. The facial sensory loss may be in an onion-skin distribution, initially sparing the nasal tip and perioral region. Hypoglossal weakness and atrophy may occur. Facial myokymia is an unusual feature. There may be autonomic involvement and respiratory compromise.

A strategically placed lesion involving the pyramidal decussation may cause unusual patterns of weakness. The corticospinal fibers innervating the upper extremities are thought to decussate more rostrally and medially than the fibers innervating the lower extremities, although this concept has been questioned (Figure 11.12). The term cruciate paralysis is used in two ways. One refers to weakness of both arms, brachial diplegia, with relative sparing of the legs, due to a lesion involving the rostral portion of the pyramidal decussation. The findings are similar to those of a central cord syndrome of the cervical spine or the man-in-the-barrel syndrome because of watershed cerebral infarction. Most cases are due to trauma. The other use refers to corticospinal paralysis of one arm and the opposite leg (cruciate hemiplegia, pyramidal decussation syndrome). This may occur because a lesion involves arm fibers that have already decussated but leg fibers that have not, which causes a crossed pattern of weakness. Triparesis, with weakness of one arm and both legs, has been reported after unilateral medial medullary infarction.

Gerstman-Sträussler-Schinker (GSS) syndrome is a rare autosomal dominant spongiform encephalopathy due to a mutation of the prion protein gene. It begins in midlife and runs a progressive course with ataxia, spasticity, dysarthria, nystagmus, and dementia. GSS is genetically and phenotypically heterogeneous; among the different prion diseases, it has the longest clinical course and the potential to mimic other neurologic disorders, such as cerebellar degeneration and demyelinating disease.

Basilar artery (Bickerstaff’s, basilar type, vertebrobasilar, posterior fossa) migraine is an unusual type of complicated migraine with prominent brainstem symptoms similar to those of VBI. The disorder occurs primarily in young females and is usually followed by an occipital headache.

The foramen magnum syndrome can cause some unusual and puzzling clinical deficits. Lesions in the region of the foramen magnum are typically compressive extramedullary mass lesions (e.g., meningioma). Patients may have

crossed hemiparesis, involving one arm and the opposite leg, because of involvement of the pyramidal decussation (see above). There may be weakness and wasting of the small hand muscles for reasons that remain unclear. Such hand muscle wasting may also occur as a false localizing sign in upper cervical spinal cord compression. Downbeat nystagmus in primary gaze is suggestive of a lesion at the cervicomedullary junction, and the nystagmus is often greatest in eccentric downgaze. Other symptoms suggestive of a foramen magnum lesion include occipital headache, neck pain, and stiffness; Lhermitte's sign; C2 sensory loss; and shawl distribution upper extremity sensory loss. Tumors are generally histologically benign and often become large before the diagnosis is made. Masses usually intrude from posteriorly, so that posterior column signs, including pseudoathetosis, are common. Lower CN palsies are uncommon. There may be a fluctuating course simulating MS.

## Bulbar Palsy

There are two principal types of bulbar palsy: PBP and pseudobulbar palsy. In both, the outstanding symptoms are dysphagia and dysarthria; both run a chronic course. Despite the similarities, the etiologies are different.

PBP is a form of motor neuron disease involving bulbar innervated muscles, causing weakness and atrophy of muscles supplied by the lower CNs, often accompanied by fasciculations. It is closely related to progressive spinal muscular atrophy, in which the process is limited to the anterior horn cells of the spinal cord, and amyotrophic lateral sclerosis (ALS), in which there is involvement of the bulbar nuclei, the anterior horn cells, and the pyramidal cells in the motor cortex.

In PBP, there is a relentlessly progressive degeneration of the neurons of the brainstem motor nuclei, primarily those in the medulla. It usually occurs in late adult life with onset in the sixth and seventh decades. The disease usually starts in the nucleus of the CN XII and ascends. Typical initial manifestations are atrophy, weakness, and fasciculations of the tongue. Involvement is bilateral from the outset. In advanced cases, the patient may be unable to protrude the tongue or to manipulate food in the mouth. The lingual involvement is followed or accompanied by dysphagia and dysarthria. Nasal regurgitation of liquids is common and may lead to choking and aspiration. Involvement of the soft palate, larynx, and tongue causes flaccid dysarthria. Early, the most pronounced difficulty is with pronunciation of linguals and velars; later, the labials are

affected. In advanced cases, speech is reduced to unintelligible laryngeal noises. There is often marked drooling of saliva. Patients may keep a tissue or rag at the chin to absorb unswallowed secretions. Sometimes, atrophy and fasciculations extend to the palate and pharynx, and the condition may eventually ascend to involve the facial and trigeminal motor nuclei. Occasionally, the sternocleidomastoid and trapezius muscles are affected. There may be autonomic involvement with tachycardia. The palatal and pharyngeal gag reflexes disappear early. There are no sensory changes. PBP is aggressive and relentless, with death usually caused by aspiration pneumonia. PBP may be the first manifestation of ALS. When ALS causes prominent bulbar weakness, it is referred to as bulbar ALS. In bulbar palsy due to ALS, there are also corticospinal tract manifestations. In a series of 32 patients with PBP, all but two progressed to ALS, regardless of the presence of upper motor signs or generalized denervation on limb electromyography (EMG). The other two died at the PBP stage.

Severe bulbar involvement occurs in other motor neuronopathies. It is often the terminal aspect of Werdnig-Hoffmann disease (hereditary spinal muscular atrophy type 1). Fazio-Londe disease is PBP occurring in children. Kennedy's disease (X-linked recessive bulbospinal neuronopathy) causes a clinical picture resembling ALS but with slow progression and other atypical features; dysphagia or dysarthria may be prominent late in the course. Bulbar polioencephalitis may occur as part of paralytic poliomyelitis, causing paralysis of the throat, tongue, and respiratory muscles. Creutzfeldt-Jakob disease may present as bulbar palsy.

Pseudobulbar palsy also causes marked difficulty with bulbar function, especially speech and swallowing. Although the clinical manifestations are similar, the underlying mechanism is entirely different. Pseudobulbar palsy is caused by bilateral supranuclear lesions, which involve the corticobulbar pathways to the bulbar nuclei. PBP and bulbar ALS cause lower motor neuron weakness; pseudobulbar palsy causes upper motor neuron weakness. In patients with bulbar ALS, both processes may be at work. Because of bilateral supranuclear innervation, unilateral lesions of the corticobulbar tract rarely cause significant bulbar dysfunction. But with bilateral supranuclear lesions, the bulbar dysfunction may be severe. It is usually accompanied by other upper motor neuron signs. There may be weakness and spasticity of the muscles of mastication, an exaggerated jaw jerk, and frontal release signs such as snout and suck reflexes. Difficulty with emotional control causing spontaneous, unprovoked laughing and crying (pseudobulbar affect, emotional incontinence)

is common. Pathologic laughing (crazy laughter or “fou rire prodromique”) and crying have also been reported with brainstem lesions. Some patients have paresis of the muscles of facial expression causing masking of the facies. There are typically significant neurologic abnormalities beyond the distribution of the CN nuclei, with bilateral cortical spinal tract signs.

The most common cause of pseudobulbar palsy is multiple cerebral infarctions. The syndrome may also occur in encephalitis, MS, trauma, cerebral anoxia, primary lateral sclerosis, or other disease processes that cause bilateral corticobulbar tract lesions. The lesions may be in the cortex or in the corona radiata, internal capsule, cerebral peduncles, or brainstem rostral to the nuclear centers. Speech is thick and slurred but may have an explosive quality. There may be dysphagia, nasal regurgitation, choking, and drooling. Patients may keep food in the mouth for prolonged periods. There is less of a tendency to choke than in true bulbar palsy because the gag reflexes are intact and may be hyperactive. Although the tongue may be strikingly immobile, atrophy and fasciculations do not develop. The prognosis in pseudobulbar palsy is no more favorable than in PBP. The eventual outcome in both conditions is death, often because of aspiration. Two types of pseudobulbar palsy have been described; one is due to lesions affecting the corticobulbar fibers, and the other is due to involvement of the basal ganglia or extrapyramidal pathways. In striatal pseudobulbar palsy, there are additional signs of basal ganglia involvement, including rigidity, hyperkinesias, and a parkinsonian picture.

Other conditions that may cause prominent weakness of bulbar muscles or other evidence of brainstem dysfunction include neuromuscular transmission disorders, some neuropathies and myopathies, and certain rare neurologic conditions. The dysarthria and dysphagia of myasthenia gravis (MG) may resemble bulbar palsy. Early in the course, it may be difficult to distinguish bulbar ALS or PBP from MG. The characteristic eye signs of MG are not always present. Bulbar signs and symptoms similar to those of MG can occur in botulism and Lambert-Eaton syndrome.

Patients with MUSK antibody MG tend to have prominent bulbar dysfunction, neck and shoulder girdle weakness, and respiratory symptoms and may develop muscle atrophy. Bulbar muscle weakness can occur in muscular dystrophies, especially oculopharyngeal dystrophy, and other myopathies. Bulbar weakness may complicate Guillain-Barré syndrome and other polyneuropathies. CN involvement is characteristic of diphtheritic polyneuropathy. In tetanus, pharyngeal spasms may accompany trismus. In

rabies, spasmodic contractions of the muscles occur on attempts to swallow. Whipple's disease involving the central nervous system (CNS) may have prominent brainstem findings. Oculomasticatory myorhythmia, a striking movement disorder involving the eyes and jaw, is characteristic, perhaps pathognomonic, of CNS Whipple's disease. Brainstem involvement may be a striking feature of Leigh's disease (subacute necrotizing encephalomyopathy). The brainstem can also be damaged by radiation.

## MULTIPLE CRANIAL NERVE PALSIES

Intracranial-extramedullary or extracranial processes may involve more than one CN. A disease may involve homologous nerves on the two sides (e.g., bilateral facial palsy) or different nerves on the same or opposite sides. In some conditions, a cluster of nerves is involved in a discrete anatomical region. The progression may follow some anatomical pattern or appear capricious. Multiple CNs may be affected from the outset, or the process may begin with one nerve and progress to involve others. Pain may or may not be present. Table 21.3 lists some conditions that may cause MCNPs. Table 21.4 covers some of the named multiple CN syndromes.

In Keane's series of 979 patients with MCNP, the most commonly involved nerves were CNs VI, VII, V, and VIII. The most common combinations were involvement of CNs III and IV, V and VI, and V and VII. The most common locations were cavernous sinus, brainstem, and individual nerve trunks. The most common causes were neoplasm, vascular disease, trauma, infection, and the Guillain-Barré and Miller Fisher syndromes. A MCNP variant of Guillain-Barré has been described. The most common causes of recurrent cranial neuropathies were diabetes and idiopathic.

A major consideration when there is MCNP is some process affecting the meninges at the base of the skull. Although infectious and inflammatory conditions are possible, the major consideration when there is painless dysfunction of several CNs over a period of days to weeks is neoplastic meningitis, which can be either carcinomatous or lymphomatous (meningeal carcinomatosis or lymphomatosis). Neoplastic meningitis occurs in as many as 15% of patients with systemic malignancy and may be the presenting manifestation in 5% to 10%. The most common neoplastic processes to involve the meninges are small cell carcinoma of the lung, melanoma, and myeloblastic

leukemia. Carcinoma of the breast seldom spreads to the meninges but is a common cause of meningeal neoplasia because of its frequency.

**TABLE 21.3 Some Disease Processes That May Involve Multiple Cranial Nerves (CNs)**

- Acute infectious meningitis
- Chronic infectious meningitis
- Syphilis
- Lyme disease
- Viral infection (Herpes zoster, herpes simplex, EBV, HIV, HTLV-1, CMV)
- Meningeal neoplasia (leptomeningeal metastases, carcinomatous meningitis, lymphomatous meningitis, primary leptomeningeal lymphoma, neurolymphomatosis)
- Pituitary apoplexy
- Nasopharyngeal carcinoma (Schmincke tumor)
- Primary clivus or skull base neoplasm (glomus tumor, meningioma, chordoma, others)
- Metastatic clivus or skull base neoplasm (prostate, breast, lung, head, and neck tumors)
- Cavernous sinus disease (Tolosa-Hunt syndrome, mass lesion, others)
- Sarcoidosis (special predilection for CNs II, VII, and VIII)
- Granulomatosis with polyangiitis (Wegener's granulomatosis)
- Vasculitis (polyarteritis nodosa, Churg-Strauss, lymphomatoid granulomatosis, giant cell arteritis, granulomatous angiitis)
- Connective tissue disease (systemic lupus erythematosis, Sjögren's syndrome, scleroderma, mixed connective tissue disease)
- Cryoglobulinemia
- Prepontine mass lesion
- Skull base trauma
- Aneurysm (carotid dissection, fusiform basilar)
- Carotid endarterectomy
- Bony disease of skull base (Paget's disease, osteopetrosis)

| |
|---|
| Diabetes mellitus |
| Guillain-Barré syndrome |
| Miller Fisher syndrome |
| Polyneuritis cranialis |
| Amyloidosis |
| Craniocervical junction anomalies |
| Cranial irradiation |
| Idiopathic cranial polyneuropathy |
| Idiopathic hypertrophic cranial pachymeningitis |

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HTLV-1, human T-cell lymphocytotrophic virus.

Patients with neoplastic meningitis typically have accompanying headache, meningeal signs, and evidence of increased intracranial pressure. Facial numbness in association with a multiple lower CN palsy syndrome is ominous. A combination of CNs VI and XII palsies is particularly suggestive of a neoplastic process involving the clivus. Leptomeningeal metastatic disease from solid tumors is more likely to present with spinal cord or radicular involvement. Diffuse meningeal involvement from hematologic malignancies is more likely to present with MCNP. Obtaining CSF cytologic confirmation is often difficult initially; biochemical markers may be helpful.

**TABLE 21.4 Summary of Syndromes with Involvement of Multiple CNs***

| Syndrome | Lesion Location | Structures Involved | Clinical Findings | Comment |
|---|---|---|---|---|
| Superior orbit fissure (Rochon-Duvigneau) | Superior orbital fissure | CNs III; IV; VI; $V_1$ | Weakness of CNs III, IV, VI; sensory loss in $V_1$ distribution; +/– proptosis | Usually due to tumor or carotid aneurysm |
| Orbital apex | Orbital apex | Same as superior orbital fissure plus CN II | Same as superior orbital fissure plus visual impairment due to CN II involvement | Usually due to tumor, aneurysm, or inflammatory process (orbital pseudotumor) |
| Orbital floor (Dejean's) | Orbital floor | Ocular motor nerve or extraocular muscle, $V_2$ | Diplopia, $V_2$ sensory loss, exophthalmos | Mass lesion or blowout fracture of floor of orbit |
| Cavernous sinus (Foix-Jefferson) | Cavernous sinus | CNs III; IV; VI; $V_1$, +/–$V_2$; pericarotid sympathetics | Weakness of CNs III, IV, VI; sensory loss in $V_1$ distribution; +/– proptosis | Common causes include granulomatous inflammation (Tolosa-Hunt syndrome), tumor, and aneurysm |
| Retrosphenoid space (Negro-Jacod) | Retrosphenoid space | CNs II; III; IV; V, VI | Dysfunction of listed nerves | Usual cause is large middle fossa neoplasm |
| Petrous apex (Gradenigo's) | Apex of the petrous bone | CNs V; VI | Sixth nerve palsy and facial pain and/or numbness | Usual causes are inflammation (*apex petrositis*) and tumor |
| Cerebellopontine angle | Cerebellopontine angle | CN VIII; +/–VII; +/–V; +/– cerebellar hemisphere | Hearing loss; imbalance; facial sensory loss; large tumors may cause facial weakness, ataxia, increased ICP | Usual cause is acoustic neuroma; other mass lesions may produce the same picture (e.g., meningioma) |
| Jugular foramen (Vernet's) | Jugular foramen | CN IX; X; XI | Weakness in the distribution of involved nerves | Usual causes are tumor of jugular bulb, aneurysm, and trauma (e.g., basilar skull fracture) |
| Collet-Sicard (MacKenzie, Lannois-Jouty) | Posterior lateral condylar space | CN IX; X; XI; XII | Weakness in the distribution of involved nerves | Usually due to neoplasm of the skull base, especially glomus jugulare tumor; occasionally carotid aneurysm (including dissection) |
| Villaret's | Retropharyngeal space | CNs IX; X; XI; XII; carotid sympathetics | Weakness in the distribution of involved nerves; Horner's syndrome | Usually due to neoplasm of the skull base, especially glomus jugulare tumor, occasionally carotid aneurysm (including dissection) |
| Tapia's | Retroparotid space | CNs X; XII; +/–XI; carotid sympathetics | Weakness in the distribution of involved nerves; Horner's syndrome | Usually due to tumor of parotid or skull base; occasionally carotid aneurysm (including dissection) |
| Garcin's (half-base) | Skull base | Variable CNs III–XII | Unilateral paralysis of all or most of the cranial nerves; occasionally bilateral | Usually due to tumor of the skull base, nasopharynx, or retropharyngeal space; can be due to granuloma or infection |

*Most are due to disease extracranially in the region of the skull base. Some are more commonly known by their anatomic description (e.g., jugular foramen syndrome) and some by their eponym (e.g., Collet-Sicard syndrome). In some instances, the anatomic designation is reasonably precise and appropriate (e.g., cavernous sinus syndrome). In others, the anatomical description is cumbersome or obscure, and the eponym is more convenient. The table lists the usage likely to be most familiar to most readers first.

CN, cranial nerve; ICP, increased intracranial pressure.

Other neoplastic processes and mass lesions at the base of the skull may also produce an MCNP syndrome. A skull base neoplasm accounted for 13% of cases in Keane's MCNP series. Nasopharyngeal carcinomas (NPCs), such as lymphoepithelioma (Schmincke tumor), occur in younger patients than do other head and neck cancers; there may be an association with Epstein-Barr virus infection. NPC often arises in Rosenmuller's fossa and spreads laterally to the paranasopharyngeal space and then to the skull base. The tumor may infiltrate

the pterygopalatine fossa, and the maxillary nerve, and may spread to involve the cavernous sinus. About 20% of patients have CN involvement at the time of the diagnosis of NPC. Radiotherapy for the tumor may itself cause cranial neuropathy, particularly of CN XII. Distinguishing radiation-induced neuropathy from tumor recurrence may be difficult.

NPCs may erode the clivus. Other tumors involving the clivus may also cause MCNP. A chordoma, a rare primary bone tumor, usually presents in males in the sixth decade. The tumor is histologically benign but locally invasive and destructive. When it extends posteriorly, it may cause CN palsies or brainstem compression. Other skull base neoplasms include metastasis, meningiomas, lymphoma, myeloma, histiocytosis, neurinoma, giant cell tumor, hemangiopericytoma, and various primary bone tumors. Osteopetrosis (Albers-Schonberg or marble bone disease) causes a generalized increase in bone density and can narrow exit foramina, causing MCNP. Other bone disorders that may behave similarly include Paget's disease, fibrous dysplasia, and hyperostosis cranialis interna.

Mass lesions lying along the clivus, even though not arising from it directly, may cause MCNP. Vertebrobasilar dolichoectasia may cause cranial neuropathies because of compression or ischemia. Patients with a tortuous basilar artery of normal caliber are more likely to have isolated cranial neuropathy; those with basilar artery ectasia or with fusiform, giant aneurysm are more likely to have MCNP. Rarely, hematoma lying along the clivus in the prepontine region affects multiple CNs. Other processes that may affect the prepontine region include exophytic glioma and dermoid, epidermoid, and other cystic lesions.

Infectious disease accounted for 10% of Keane's MCNP cases. Conditions particularly prone to cause cranial neuropathy include Lyme disease, tuberculosis, neurosyphilis, cryptococcosis, and HIV.

The nervous system is involved in 5% to 15% of patients with sarcoidosis. The disease may present neurologically and rarely remains confined to the nervous system. About half of the patients with neurosarcoidosis have CN involvement. The CNs most commonly involved are II, VII, and VIII. A peripheral facial palsy is the most common manifestation. About half of the patients with CN involvement have a cranial polyneuropathy, most commonly bilateral facial nerve palsy. Other common neurologic complications include chronic meningitis, hydrocephalus, hypothalamic-pituitary dysfunction, myelopathy, myopathy, and peripheral neuropathy. Neurologic involvement

occurs in as many as 20% of patients with Behcet's disease, including MCNP due to meningeal or brainstem lesions. The most commonly involved nerves are CN II and CN VIII.

Several forms of systemic vasculitis may cause MCNP; the most common is granulomatosis with polyangiitis (Wegener's granulomatosis). In one series, cranial neuropathies were the most common neurologic abnormality. Giant cell arteritis may cause the combination of optic and extraocular neuropathies. Other vasculitic processes of concern include lymphomatoid granulomatosis, a lymphoreticular malignancy, and vasculitis due to connective tissue disease, especially polyarteritis nodosa.

Polyneuritis cranialis is an MCNP syndrome that may represent a variant of Guillain-Barré syndrome involving the lower CNs. An acute, painful, steroid-responsive MCNP syndrome that may be on a continuum with Tolosa-Hunt syndrome (see section on Cavernous Sinus Syndrome) but involving nerves outside the cavernous sinus has been described (idiopathic cranial polyneuropathy). Bannwarth's syndrome (meningopolyradiculitis) refers to MCNP and painful polyradiculopathies due to Lyme disease. Most patients have an acute peripheral facial paresis with additional involvement of other nerves and spinal roots.

CN palsy occurs occasionally in carotid artery dissection; rarely, it is the dominant or only manifestation. Ipsilateral headache, Horner's syndrome, and lower CN palsy are suggestive of carotid dissection even in the absence of cerebral ischemic symptoms. CN XII is invariably affected, and in some patients, other CNs may be involved as well. The etiology is not certain. There may be compression or stretching by the aneurysmal dilatation or ischemia due to involvement of the segmental arteries supplying the nerves, particularly the ascending pharyngeal artery. CN palsy also occurs as a complication of carotid endarterectomy.

Trauma accounted for 12% of MCNP cases in Keane's series. Blunt trauma, such as MVA or falling, is twice as common as penetrating trauma. Iatrogenic trauma accounts for a significant minority, especially radical head or neck dissections.

## DISORDERS OF CRANIAL NERVE GROUPS

In some locations, two or more CNs are bundled in a common anatomical space,

such as the cavernous sinus or jugular foramen. A focal disease process may involve the entire cluster of nerves. Intradural, extramedullary pathology involves the nerves after they exit the brainstem but before they exit the skull (e.g., in the cerebellopontine angle [CPA]). Extracranial pathology involves a group of nerves just after they exit the skull but before they disperse (e.g., in the retroparotid space). As with brainstem syndromes, the many syndromes that involve multiple CNs carry an eponym and an anatomical description. The anatomical regions involved are often so arcane that the eponym serves just as well. Table 21.4 summarizes these syndromes. Most of the disorders affecting CN groups are due to mass effect. The mass is often neoplastic. Primary neural tumors, such as schwannoma or neurofibroma, arising from one CN may cause compression of adjacent nerves. Many of these syndromes are rare in neurologic practice. The relatively common ones are the cavernous sinus, CPA, and jugular foramen syndromes.

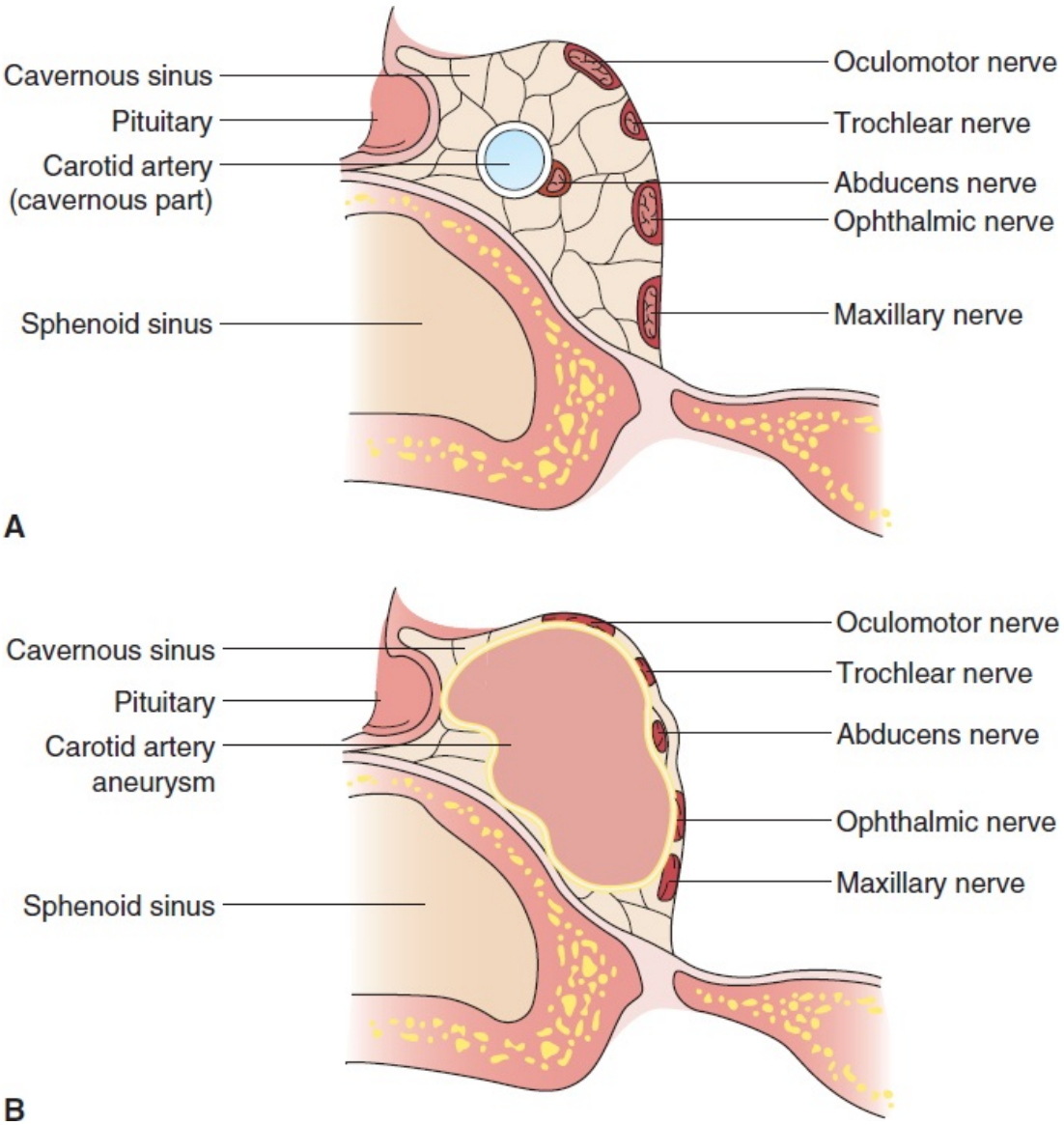


**FIGURE 21.3** **A.** The cavernous sinus lies just lateral to the sella turcica. Within it lie the carotid artery and cranial nerves (CNs) III, IV, and VI and branches of CN V. **B.** Pathologic findings involving the cavernous sinus are not rare and can usually be recognized by the pattern of CN involvement.

## Cavernous Sinus Syndrome

The cavernous sinuses are complex venous channels that lie on either side of the sphenoid bone and sella turcica, extending from the superior orbital fissure to the apex of the petrous temporal bone (Figure 21.3). The two sides are connected by an anterior and posterior intercavernous sinus. A thin layer of dura, the pituitary capsule, forms the medial wall of the cavernous sinus. The internal carotid artery with its pericarotid sympathetic plexus runs through the sinus. CNs III, IV, and V

lie in the wall of the sinus from above to below. CN VI lies free in the lumen of the sinus inferolateral to the carotid artery. The ophthalmic division of CN V traverses the sinus; the maxillary division runs for a short distance through its posterior-inferior part.

Conditions of the cavernous sinus were recognized by Gowers in 1888, but some years later, the writings of C. Foix (French neurologist) and G. Jefferson (English neurosurgeon, best known for describing C1 fracture) brought wide recognition to the existence of the cavernous sinus syndrome. The cavernous sinus may be involved by tumor, thrombosis (bland or septic), carotid aneurysm, carotid-cavernous fistula, inflammation, infection, and other processes. There is variable involvement of the CNs crossing the sinus. Severe processes may affect all of the nerves, but isolated sixth nerve palsy also occurs. In Keane's series of 151 patients, the most common etiologies were tumor, trauma, self-limited inflammation, carotid aneurysms and fistulas, and infection. These accounted for 88% of the cases. Other causes of cavernous sinus syndrome include pituitary apoplexy, metastasis, lymphoma or leukemia, myeloma, neuroblastoma, mucormycosis, aspergillosis, tuberculosis, carotid-cavernous fistula, trauma, and sarcoidosis.

Intracavernous carotid aneurysms may compress and distort the contents of the cavernous sinus (Figure 21.3B). A carotid-cavernous fistula is a communication between the carotid artery and the cavernous sinus. Fistulas may be traumatic or develop spontaneously because of rupture of an intracavernous carotid aneurysm. In addition to CN palsies, patients may have pulsatile proptosis, chemosis, an ocular bruit, and evidence of increased venous pressure in the eye. Dilated, arteriolized conjunctival and episcleral blood vessels with a tortuous, corkscrew shape are characteristic (Figure 21.4). Neoplasms commonly involve the cavernous sinus. Common tumor types include NPC, metastases, lymphoma, pituitary adenoma, and meningioma.

Two neurosurgeons, E. S. Tolosa (Spanish) and W. E. Hunt (American), described indolent, idiopathic, granulomatous inflammation of the cavernous sinus causing pain and ophthalmoplegia. Pathologically, there is noncaseating, granulomatous inflammation similar to that seen in orbital pseudotumor. Patients present with severe periorbital headache and dysfunction of one or more of the intracavernous CNs. Tolosa-Hunt syndrome is exquisitely responsive to even small doses of steroids, and steroid responsiveness has been used as a diagnostic criterion. However, other conditions involving the cavernous sinus, including tumors, infection, and aneurysm, may also improve with steroids. MRI may

show T2 isointense tissue that enhances with gadolinium. Another condition related to cavernous sinus syndrome is Raeder's paratrigeminal (or the paratrigeminal oculosympathetic) syndrome (Chapter 15).

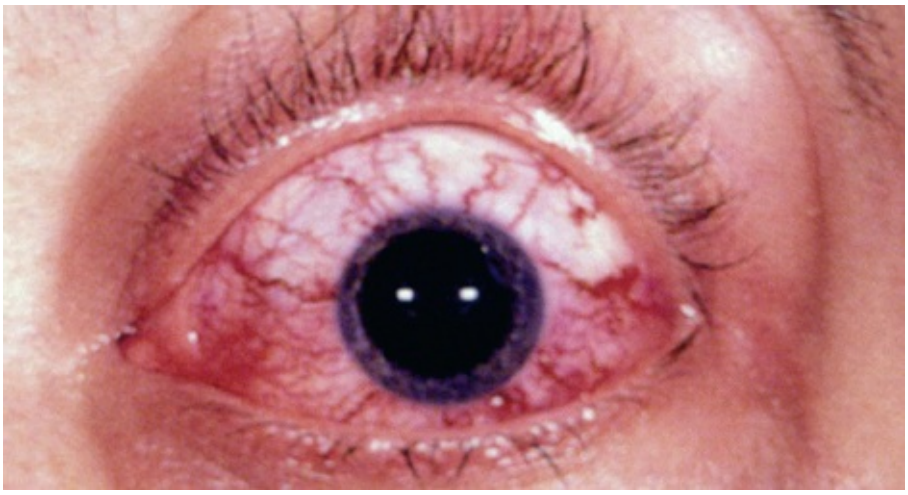

**FIGURE 21.4** Corkscrew conjunctival and episcleral vessels in a patient with a carotid-cavernous fistula.

## Cerebellopontine Angle Syndrome

A mass lesion in the CPA is usually an acoustic neuroma, but other tumors and masses may arise in the region (Chapter 17). An acoustic neuroma usually arises from the vestibular portion of CN VIII within the internal auditory meatus. The initial symptoms are usually hearing loss and tinnitus. Examination early in the course shows sensorineural hearing loss and impaired labyrinthine function on the involved side. Vertigo is unusual because the tumor grows slowly and the vestibular system compensates, although patients may have impaired balance. As the mass expands, compression of CN V causes ipsilateral facial sensory loss and impairment of the corneal reflex. Pressure on the cerebellum or its peduncles causes ataxia and incoordination. There may be involvement of CN VII, with a peripheral facial palsy, and of CNs VI, IX, and X. Late in the course, increased intracranial pressure may cause headache, papilledema, and occasional loss of consciousness. Nystagmus is common; it may be coarse and slow on gaze toward the side of the lesion (gaze paretic nystagmus) and fine and rapid on gaze away from the lesion (vestibular nystagmus). This unusual combination is referred to as Bruns' nystagmus (for Ludwig Bruns, German neurologist, see **Video Link 21.1**).