RadioGraphics

Intracranial Causes of Ophthalmoplegia: The Visual Reflex Pathways[1]

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ONLINE-ONLY SA-CME

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LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the cranial nerves involved in vision and the visual reflex pathways in terms of anatomy and function.
- List the intracranial diseases that can affect these cranial nerves and visual reflex pathways, resulting in dysfunction of the visual system.
- Discuss the correlation of patient symptomatology with the likely region of disease involvement for appropriate tailoring of the imaging examination.

TEACHING POINTS

See last page

The gathering of visual information is a complex process that relies on concerted movements of the eyes, and cranial nerves II–VIII are at least partially involved in the visual system. The cranial nerves do not function in isolation, however, and there are multiple higher-order cortical centers that have input into the cranial nerves to coordinate eye movement. Among the functions of the cortical reflex pathways are *(a)* controlling vertical and horizontal gaze in response to vestibular input to keep the eyes focused on an object as the head moves through space, and *(b)* controlling rapid, coordinated eye movement to a new visual target (saccades). There are also reflex pathways connecting the cranial nerves involved in vision that produce consensual blinking of the eyes in response to corneal stimulation of one eye and consensual pupillary constriction in response to light input on one pupil. A variety of intracranial pathologic conditions, including benign and malignant neoplasms, infection, trauma, autoimmune diseases, vascular anomalies, degenerative diseases, and inherited-congenital disorders, can disrupt the cranial nerves and visual reflex pathways. This disruption can manifest in myriad ways—for example, as extraocular muscle paresis, afferent pupillary defect, oculosympathetic paresis (Horner syndrome), internuclear ophthalmoplegia, dorsal midbrain (Parinaud) syndrome, or loss of the corneal reflex. Knowledge of the function and anatomy of the cranial nerves and visual reflex pathways, coupled with selection of the proper magnetic resonance pulse sequence, will allow the radiologist to order appropriate imaging of the involved cranial nerve or visual reflex pathway based on the patient's symptoms and thereby play an essential role in establishing the diagnosis and planning appropriate therapy.

Abbreviations: IAC = internal auditory canal, ICA = internal carotid artery, INO = internuclear ophthalmoplegia, MLF = medial longitudinal fasciculus

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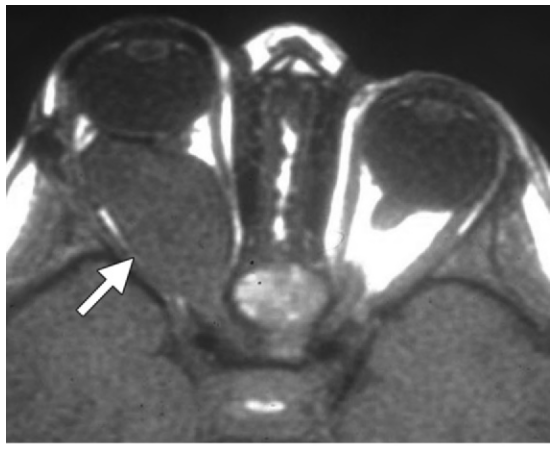
Introduction

Vision is the primary sensory mechanism mammals use to gather information about their surroundings. It is estimated that over 50% of the cortex in primates is devoted to visual processing (1). Cranial nerves II–VIII are at least partially involved in the visual system, either by controlling the globe or as part of visual reflex pathways (2). Higher-level cortical centers coordinate eye movements to *(a)* keep objects centered on the fovea as they move across the visual field, *(b)* control saccades to rapidly move the eyes to a new target, and *(c)* integrate vestibular input to retain focus on an object as the head moves through space. Numerous pathologic conditions can disrupt the neural pathways responsible for orbital control or the visual reflex centers and can manifest as a variety of entities, including ophthalmoplegia, oculosympathetic syndrome, Parinaud syndrome, and ptosis (3). A thorough clinical examination is necessary to localize the lesion, and dedicated neuroimaging may also be helpful in diagnosing the underlying cause of the visual problems and directing therapy in complex cases (4,5). Advances in magnetic resonance (MR) pulse sequences have improved anatomic detail and visualization of small structures such as the cranial nerves. In particular, the development and increased utilization of steady-state free precession imaging have provided submillimeter spatial resolution and excellent contrast between the cisternal portions of the cranial nerves and the surrounding cerebrospinal fluid (6). Familiarity with the neural centers that control vision will allow the radiologist to appropriately tailor the imaging examination and to arrive at a specific diagnosis or a reasonable differential diagnosis when encountering a visually impaired patient. In this article, we discuss the anatomy and function of the cranial nerves involved in vision and of the visual reflex pathways, as well as the spectrum of intracranial disease processes that can disrupt the visual system.

Cranial Nerves

The cranial nerves have disparate functions and histologic features; consequently, the pathologic processes that involve these nerves and the resultant neurologic deficits are also distinct.



a.

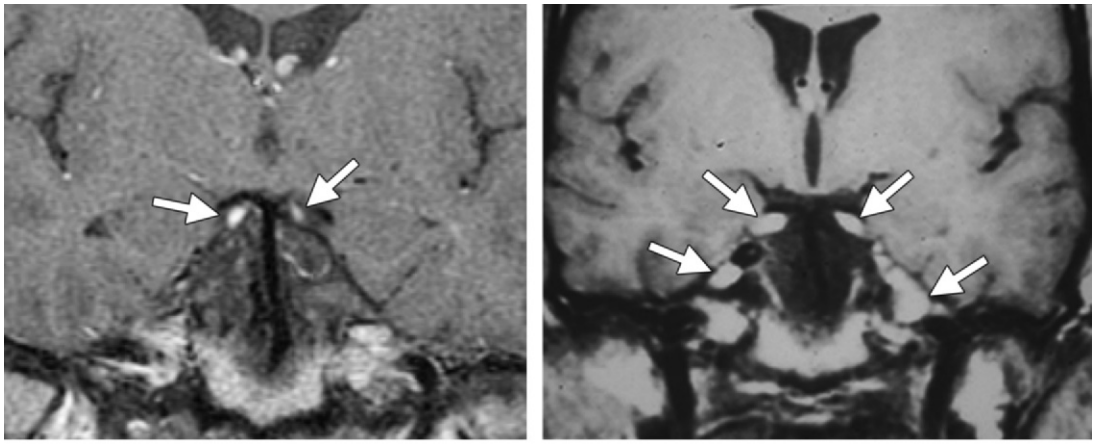
b.

Figure 1. Glioma in a 17-month-old patient. Precontrast **(a)** and postcontrast fat-saturated **(b)** T1-weighted MR images demonstrate an expansile, enhancing optic glioma (arrow). (Case courtesy of Mahmood Mafee, MD.)

All cranial nerves are subject to influence from extrinsic lesions (eg, compression by intracranial neoplasms or aneurysms), but the intrinsic processes that affect these nerves are variable. For example, the optic nerve (cranial nerve II) is affected by pathologic lesions such as gliomas (Fig 1), demyelinating diseases, and meningiomas, whereas cranial nerves III–XII can develop schwannomas (Fig 2).

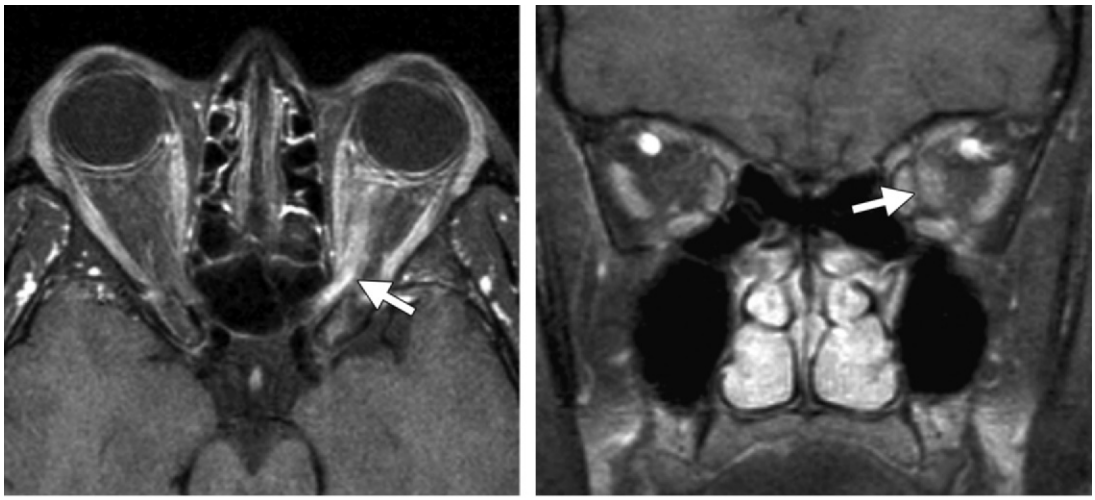
Optic Nerve (Cranial Nerve II)

The paired optic nerves consist of retinal ganglion cell axons myelinated by oligodendrocytes and enveloped within the meninges; therefore, the optic nerve is considered an extension of the brain



a. b.

Figure 2. **(a)** Coronal postcontrast T1-weighted MR image through the midbrain, obtained in a human immunodeficiency virus–positive male with multiple cranial nerve abnormalities secondary to cytomegalovirus neuritis, demonstrates abnormal enhancement of the cisternal portion of the oculomotor nerves (arrows) as they course between the posterior cerebral and superior cerebellar arteries. Cranial nerves V and VII (not shown) also demonstrated abnormal enhancement. **(b)** Coronal postcontrast T1-weighted MR image obtained in a 9-year-old patient with multiple cranial nerve palsies shows bilateral schwannomas involving multiple cranial nerves (arrows), findings diagnostic for neurofibromatosis II.



a. b.

Figure 3. Optic neuritis in a 27-year-old woman with decreased vision in the left eye. Axial **(a)** and coronal **(b)** postcontrast fat-saturated T1-weighted MR images show diffuse enhancement of the left optic nerve (arrow), a finding compatible with optic neuritis.

rather than a true cranial nerve and is subject to the same disease entities that exist elsewhere in the neuraxis (Fig 3). Cranial nerve II is responsible for relaying information from the retina to the visual cortex in an ordered fashion. Light hitting each region of the visual fields is directed to a specific location in the occipital lobe. Light initially hits the retina, and the signal generated is carried in the optic nerves, which have four segments: intraocular, intraorbital, intracanalicular, and intracranial. There is partial decussation at the chiasm, and the signal continues along the optic tracts to the lateral geniculate body of the thalamus. Fibers continue from the lateral geniculate body as the

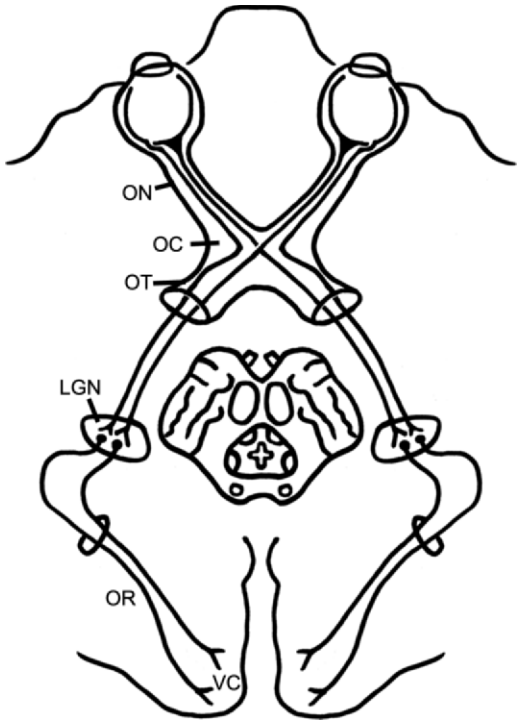


Figure 4. Drawing illustrates the visual pathway. *LGN* = lateral geniculate nucleus, *OC* = optic chiasm, *ON* = optic nerve, *OR* = optic radiation, *OT* = optic tract, *VC* = visual cortex. (Adapted, with permission, from reference 7.)

optic radiations, which relay information to the visual cortex in the occipital lobes (Fig 4) (7). The location of a visual pathway lesion will determine the extent of visual loss, with optic nerve disease leading to monocular visual problems, chiasmatic disease leading to bitemporal hemianopsia, and retrochiasmatic disease causing loss of all or part of the contralateral visual field (8).

Oculomotor Nerve (Cranial Nerve III)

The oculomotor nerve provides motor fibers to the levator palpebrae muscle (which keeps the eyelid elevated), as well as to all of the extraocular muscles except the lateral rectus and superior oblique muscles. Cranial nerve III also supplies parasympathetic fibers to internal eye muscles responsible for constriction of the pupil (pupillary sphincter and ciliary muscles) via the Edinger-Westphal nucleus. The nuclei of cranial nerve III are in the midbrain at the level of the superior colliculi, bound laterally and inferiorly by the medial longitudinal fasciculus (MLF) (discussed later) (Fig 5a). The Edinger-Westphal nuclei are located dorsally in the periaqueductal gray matter. The fibers of cranial nerve III exit the brainstem anteriorly between the posterior cerebral and superior cerebellar arteries. The parasympathetic fibers travel peripherally in the nerve and are subject to compression by extrinsic masses. The vascular supply to the nerve is contained centrally; thus, microvascular

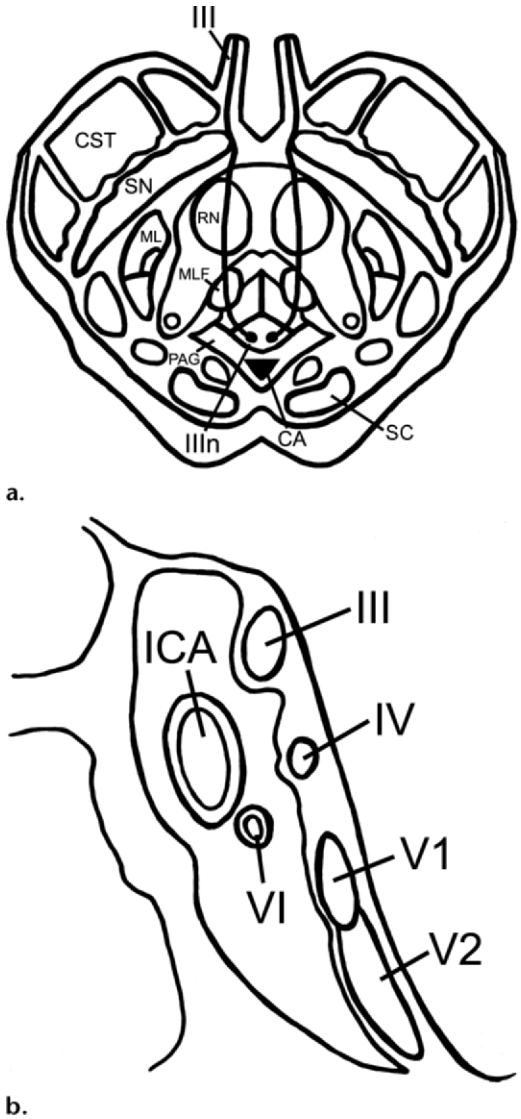
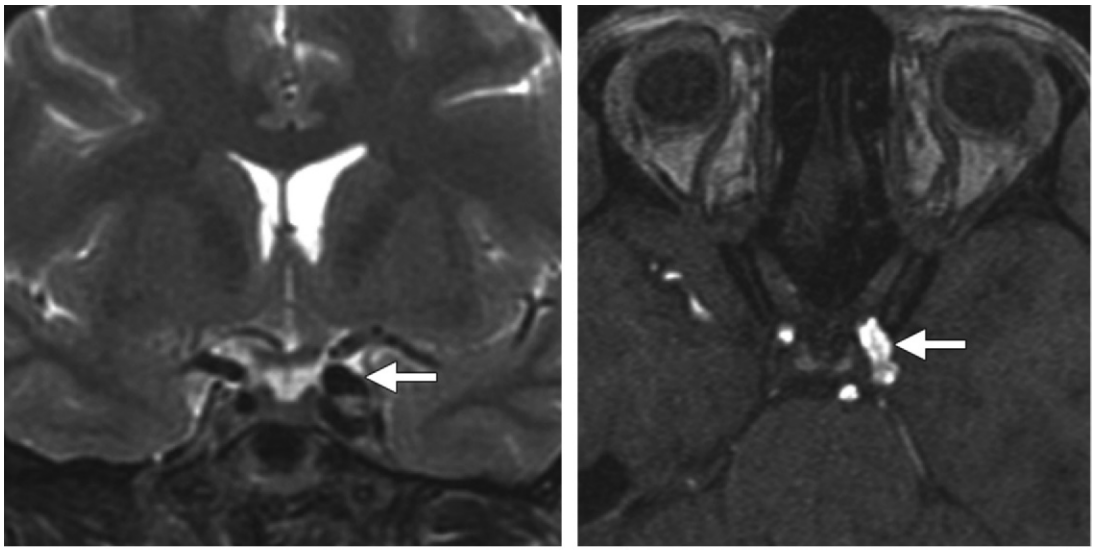
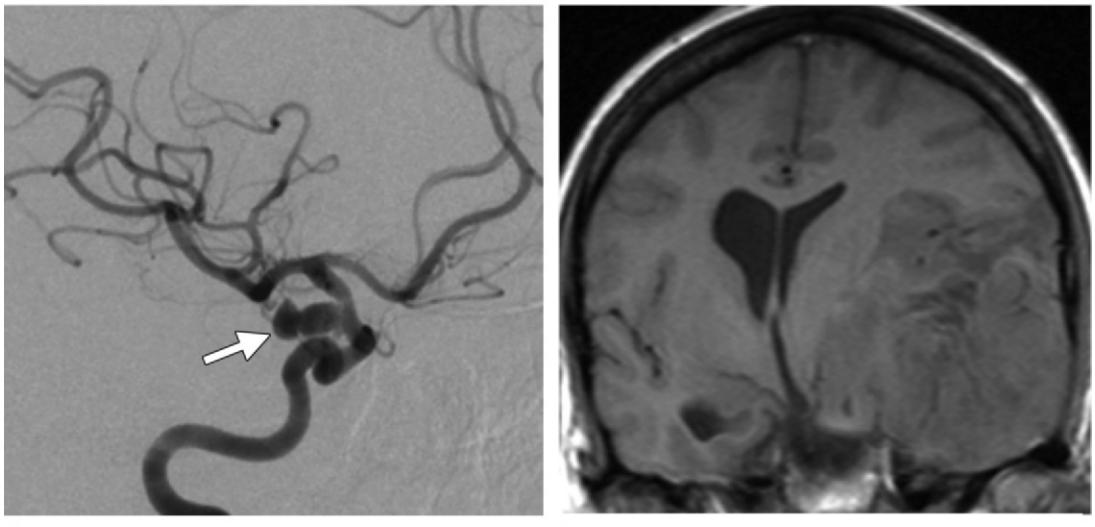


Figure 5. **(a)** Drawing illustrates the oculomotor nerve at the level of the superior colliculus. *CA* = cerebral aqueduct, *CST* = corticospinal tracts, *ML* = medial lemniscus, *PAG* = periaqueductal gray, *RN* = red nucleus, *SC* = superior colliculus, *SN* = substantia nigra, *III* = cranial nerve III, *IIIn* = cranial nerve III nucleus. (Courtesy of L. Anne Hayman, MD.) **(b)** Drawing illustrates the cavernous sinus. Cranial nerves III, IV, V1, and V2 lie within the lateral dural wall of the cavernous sinus. Cranial nerve VI lies inferolateral to the cavernous internal carotid artery (ICA). (Reproduced, with permission, from reference 9.)



6a. 6b.



6c. 7.

Figures 6, 7. **(6)** Cranial nerve III palsy in a patient who presented with inferior and lateral deviation of the left pupil. Coronal T2-weighted MR image **(a)**, axial three-dimensional time-of-flight MR angiogram **(b)**, and digital subtraction angiogram **(c)** demonstrate a left posterior communicating artery aneurysm (arrow) compressing cranial nerve III. **(7)** Cranial nerve III palsy in a 45-year-old woman with a known brain mass who presented with a dilated pupil. Coronal T1-weighted MR image shows a large left temporal oligodendroglioma causing uncal herniation and compression of the left oculomotor nerve.

compromise can cause loss of motor function in the extraocular muscles innervated by cranial nerve III with relative sparing of the pupillary parasympathetic innervation ("pupil-sparing" oculomotor palsy). The cisternal segment of cranial nerve III courses through the prepontine cistern before entering the cavernous sinus, traveling along the cephalad portion of the lateral dural wall (Fig 5b) (9). Cranial nerve III enters the orbit through the superior orbital fissure, where it divides into superior and inferior branches (8).

Teaching Point

A variety of pathologic conditions can affect cranial nerve III. Its close association with the posterior cerebral and superior cerebellar arteries makes cranial nerve III susceptible to compression by vascular lesions such as posterior communicating artery aneurysms (Fig 6) (10). The location of the nerve as it courses over the petroclinoid ligament also makes it susceptible to compression during herniation of the uncus through the tentorium cerebelli (Fig 7) (11).

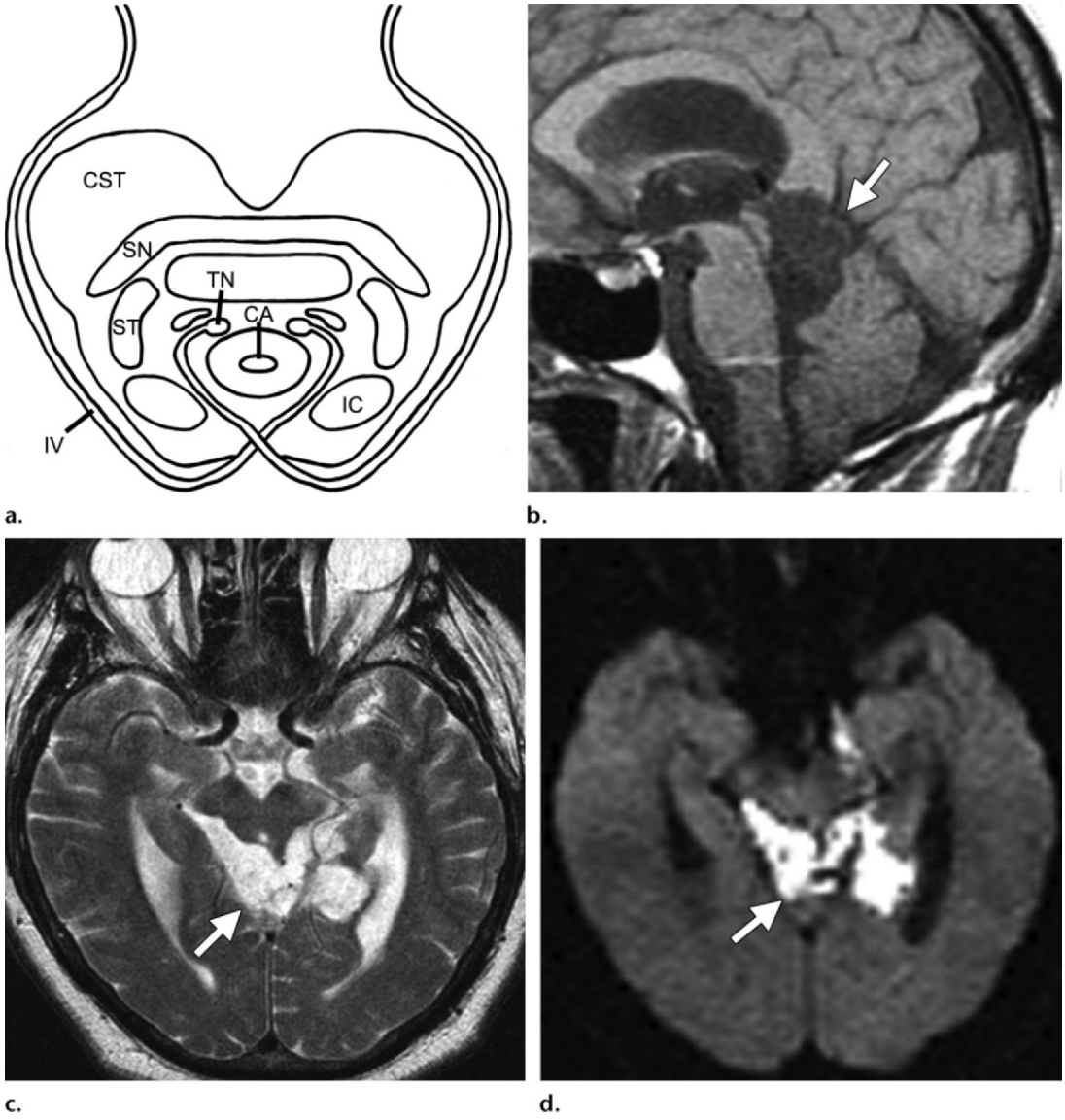
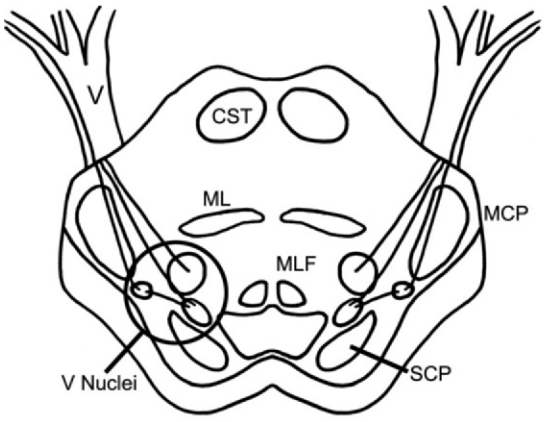


Figure 8. **(a)** Drawing illustrates cranial nerve IV nuclei in the midbrain at the level of the inferior colliculus *(IC)*. *CA* = cerebral aqueduct, *CST* = corticospinal tract, *IV* = cranial nerve IV, *SN* = substantia nigra, *ST* = spinothalamic tract, *TN* = trochlear nerve nucleus. (Courtesy of L. Anne Hayman, MD.) **(b–d)** Epidermoid tumor in a 63-year-old man who presented with intermittent diplopia and seizures. **(b, c)** Sagittal T1-weighted **(b)** and axial T2-weighted **(c)** MR images show a mass that is isointense relative to cerebrospinal fluid (arrow) compressing the left trochlear nerve in the ambient cistern. **(d)** On an axial diffusion-weighted MR image, the mass restricts diffusion (arrow), a finding that strongly supports the diagnosis of epidermoid tumor.

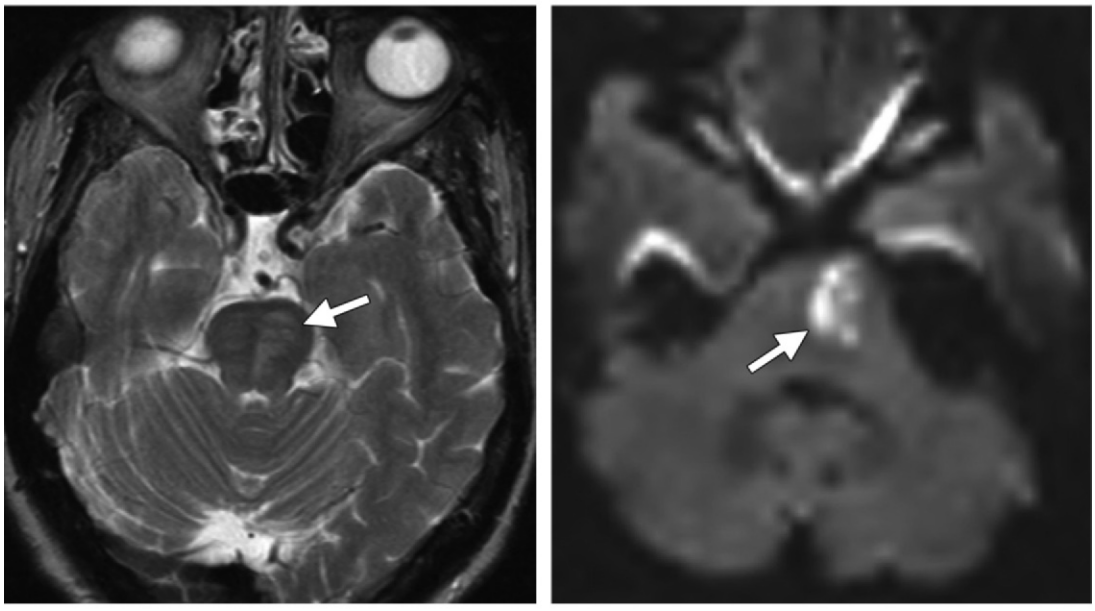
Trochlear Nerve (Cranial Nerve IV)

The fourth cranial nerve is a pure motor nerve, supplying fibers to the superior oblique muscle. The paired cranial nerve IV nuclei are located in the paramedian midbrain, and the fascicles course posteriorly and inferiorly around the cerebral aqueduct, where they decussate before exiting the dorsal midbrain. Cranial nerve IV is the only cranial nerve to exit the dorsal brainstem, and each superior oblique muscle is innervated by the contralateral cranial nerve IV nucleus (Fig 8a). The cisternal portion of cranial nerve IV courses through the ambient cistern, traveling inferolateral to cranial nerve III between the superior cerebellar and posterior cerebral arteries before entering the cavernous sinus. The trochlear nerve then passes through the superior orbital fissure, above the annulus of Zinn, and innervates the superior oblique muscles (8).

Cranial nerve IV is the smallest cranial nerve and is often not visualized directly even on thin-section images. The anatomic landmarks described earlier will help identify the course of this nerve, even if it is not directly visualized, and will



a.



b. c.

Figure 9. **(a)** Drawing illustrates the upper pons. *CST* = corticospinal tract, *V* = cranial nerve V, *V Nuclei* = cranial nerve V nuclei, *MCP* = middle cerebellar peduncle, *ML* = medial lemniscus, *SCP* = superior cerebellar peduncle. (Courtesy of L. Anne Hayman, MD.) **(b, c)** Acute infarct in a 73-year-old woman with sudden-onset weakness and left facial dysesthesias. Axial T2-weighted **(b)** and diffusion-weighted **(c)** MR images show an acute infarct (arrow) involving the left corticospinal tract and trigeminal nerve in the pons. The high-signal-intensity region on the diffusion-weighted image had low signal intensity on the apparent diffusion coefficient map (not shown).

assist in diagnosing lesions that affect its function (Fig 8b–8d) (12).

Trigeminal Nerve (Cranial Nerve V)

The trigeminal nerve provides sensation to the face and motor innervation to the muscles of mastication. Cranial nerve V has four separate nuclei (three sensory and one motor). The cisternal portion of cranial nerve V exits the lateral pons and traverses the prepontine cistern before passing underneath the tentorium to enter the middle cranial fossa at the petrous apex (Fig 9a). The preganglionic portion of cranial nerve V then passes through a dural opening known as the porus trigeminus into the Meckel cave, where it synapses with the trigeminal ganglion (also known as the gasserian or semilunar ganglion) (8). The postganglionic trigeminal nerve is subdivided into the ophthalmic (V1), maxillary (V2), and mandibular (V3) nerves. V3 exits the Meckel cave through the foramen ovale and does not traverse the cavernous sinus; V2 travels in the lateral cavernous sinus inferior to V1 and exits through the foramen rotundum. In this article, however, we focus on cranial nerve V1, which supplies sensory innervation to the scalp, forehead, nose, and globe. V1 travels within the lateral cavernous sinus inferior to cranial nerve IV and superior to V2 (Fig 5b). V1 then enters the orbit through the superior orbital fissure, where it divides into the lacrimal, frontal, and nasociliary nerves. Cranial nerve V is subject to the same spectrum of diseases as the other cranial nerves, but lesions affecting cranial nerve V will typically cause symptoms that are not confined to the globe (Fig 9b, 9c).

Abducens Nerve (Cranial Nerve VI)

Cranial nerve VI is a pure motor nerve that supplies the lateral rectus muscle. The paired cranial nerve VI nuclei are located in the pontine tegmentum near the midline. The axons of the facial nerve loop around the cranial nerve VI nuclei at the facial colliculus, causing a bulge in the floor

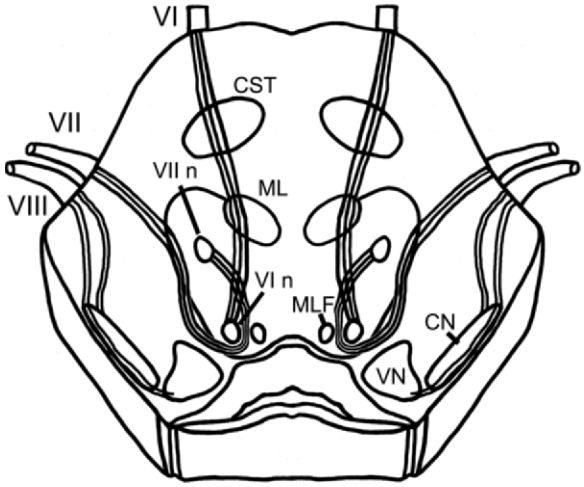
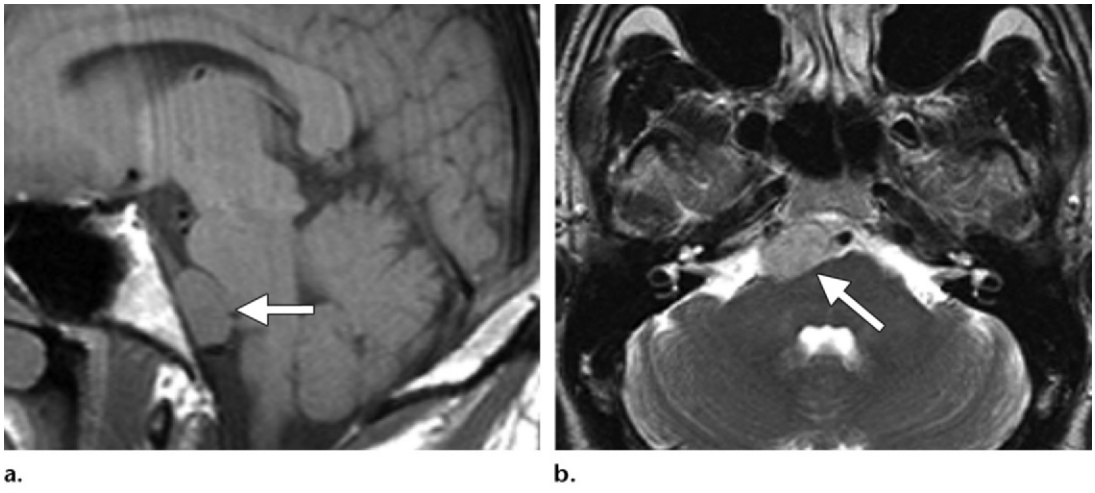
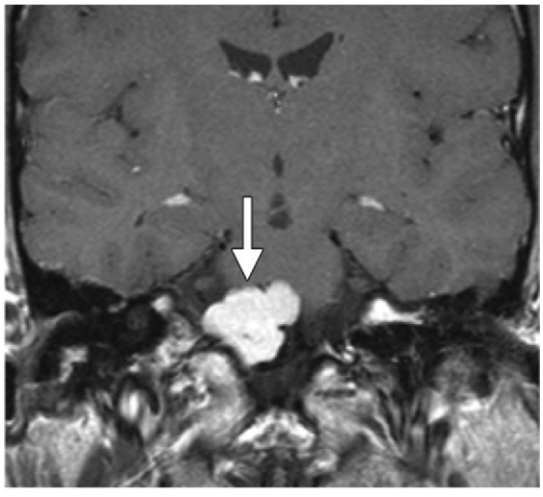


Figure 10. Drawing illustrates the lower pons. *CN* = cochlear nucleus, *CST* = corticospinal tract, *VIII* = cranial nerve VIII, *ML* = medial lemniscus, *VII* = cranial nerve VII, *VII n* = nucleus of cranial nerve VII, *VI* = cranial nerve VI, *VI n* = nucleus of cranial nerve VI, *VN* = vestibular nucleus. (Courtesy of L. Anne Hayman, MD.)



a. **b.**



c.

Figure 11. Meningioma in a 46-year-old man with right sixth nerve palsy. Sagittal T1-weighted **(a)**, axial T2-weighted **(b)**, and coronal postcontrast T1-weighted **(c)** MR images demonstrate an enhancing mass (arrow) compressing the right abducens nerve. The mass was found to represent a meningioma.

Teaching Point

of the fourth ventricle (Fig 10). The cisternal portion of cranial nerve VI exits the brainstem near the midline through the space between the pons and the pyramid of the medulla oblongata. The nerve courses anteriorly in the prepontine cistern (Fig 11) and penetrates the dura mater to enter the Dorello canal and then the cavernous sinus, where it is the only nerve to travel within the venous sinusoids of the cavernous sinus (cranial nerves III, IV, V1, and V2 all lie within the lateral dural wall of the cavernous sinus) (Fig 5b). Cranial nerve VI lies inferolateral to the cavernous ICA, then enters the orbit through the superior orbital fissure (8).

Facial Nerve (Cranial Nerve VII)

The facial nerve is a mixed nerve that is responsible for motor innervation of the muscles of facial expression (including the orbicularis oculi muscle, which is responsible for closing the eyelids), supplying taste fibers to the anterior two-thirds

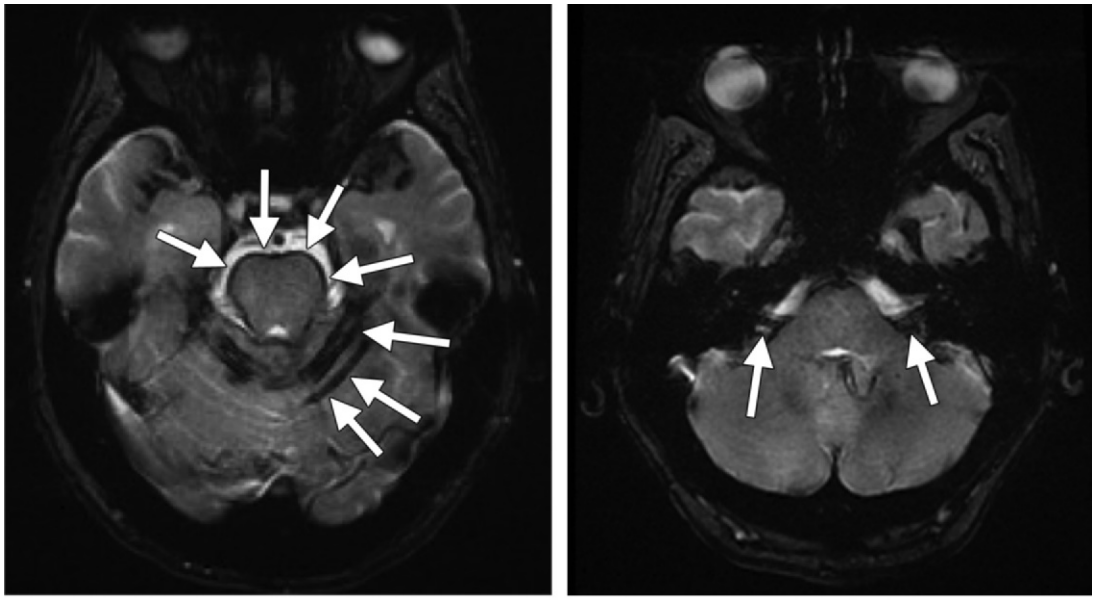
Figure 12. Bell palsy in a 72-year-old woman. Axial postcontrast T1-weighted MR image demonstrates enhancement of the canalicular and labyrinthine segments of the right facial nerve extending to the geniculate ganglion (arrow). Although the perineural plexus surrounding the facial nerve can cause some enhancement in the region of the geniculate ganglion, enhancement of the canalicular segment (as seen in this case) is abnormal.

of the tongue, and parasympathetic innervation of the lacrimal and submandibular glands. One motor nucleus and two sensory nuclei of cranial nerve VII are located within the ventrolateral pons; the fibers of cranial nerve VII loop around the abducens nucleus to form the facial colliculus and exit the lateral brainstem at the pontomedullary junction (Fig 10). Cranial nerve VII exits as two separate nerve roots (motor root anteriorly and sensory root posteriorly) and traverses the cerebellopontine angle cistern to enter the anterosuperior aspect of the internal auditory canal (IAC) above the crista falciformis. Cranial nerve VII takes a circuitous course through the temporal bone and is divided into segments. The *cisternal segment* is within the cerebellopontine angle cistern; the *canalicular segment* is within the IAC; the *labyrinthine segment* connects the canalicular segment to the geniculate ganglion, where the greater superficial petrosal nerve branches and passes anteromedially to carry parasympathetic fibers to the lacrimal gland; and the *tympanic segment* begins after the geniculate ganglion and passes under the lateral semicircular canal to the posterior genu, where the *mastoid segment* begins as cranial nerve VII travels inferiorly and gives rise to the chorda tympani. The chorda tympani in turn travels with the lingual branch of V2 to supply taste fibers to the anterior two-thirds of the tongue. The facial nerve then exits the skull via the stylomastoid foramen and enters the parotid space, branching into the terminal motor branches (8).

It is evident that the facial nerve has many important functions, but its impact on the visual system consists primarily of controlling the orbicularis oculi muscle, which is responsible for blinking to keep the cornea hydrated. There are bilateral cortical (supranuclear) neurons responsible for voluntary control of the orbicularis oculi and frontalis muscles, so that patients with stroke or some other lesion that impacts the cortical motor neurons responsible for facial control will still be able to voluntarily blink and raise the eyebrows thanks to the inputs from the unaffected motor neurons contralateral to the lesion. Conversely, the neurons responsible for motor control of the lower face do not have bilateral inputs and will therefore be affected by supranuclear lesions. This condition is sometimes referred to as "forehead sparing" in patients with supranuclear facial paralysis. Patients with Bell palsy or some other infranuclear lesion of cranial nerve VII will have paralysis of all the facial muscles, including the orbicularis oculi muscle, and are susceptible to corneal damage, pain, and resultant visual loss as the cornea dries out (Fig 12) (13).

Vestibulocochlear Nerve (Cranial Nerve VIII)

Cranial nerve VIII is a sensory nerve with two main components: *(a)* the vestibular nerve, which is responsible for balance, and *(b)* the cochlear nerve, which is responsible for hearing. In this article, we focus on the vestibular portion of cranial nerve VIII, since it plays a large role in the concerted movements of the eyes as the head moves through space (14). Unlike that of the other cranial nerves, the anatomy of the vestibular nerve is discussed from peripheral to central. The vestibular nerve arises from the Scarpa ganglion in the fundal portion of the IAC, with peripheral fibers innervating the sensory epithelium of the utricle, saccule, and semicircular canals. Central fibers coalesce to form the superior and inferior vestibular nerves, which travel in the posterior aspect of the IAC and are separated from each other by the crista falciformis. These nerves join with each other and the cochlear nerve near the opening of the IAC into the cerebellopontine angle to form the vestibulocochlear nerve. Cranial nerve VIII travels posterior to cranial nerve VII and enters the lateral brainstem, where vestibular fibers



a. b.

Figure 13. Superficial siderosis in a 75-year-old man with a history of pituitary macroadenoma and acromegaly who had undergone transsphenoidal resection. Axial gradient-echo T2*-weighted MR images demonstrate deposition of hemosiderin within the cerebellar folia and surrounding the brainstem (arrows in **a**), as well as bilateral deposition along the cisternal segments of cranial nerve VIII (arrows in **b**), findings consistent with superficial siderosis.

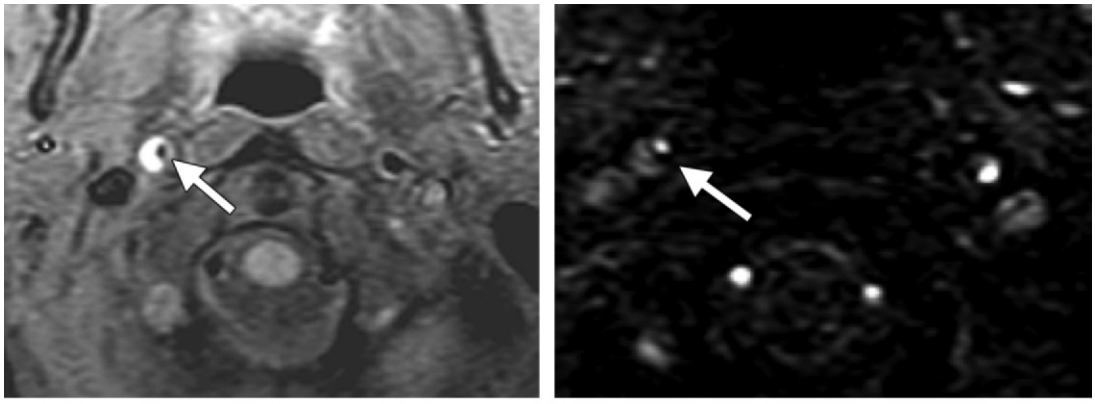
divide into ascending and descending branches. These branches terminate in the vestibular nuclear complex, which lies in the lateral recess of the floor of the fourth ventricle (8). These nuclei send fibers to the horizontal and vertical gaze centers as part of the vestibulo-ocular reflex.

The vestibulocochlear nerve may be impacted by any lesion in the cerebellopontine angle, but it is especially sensitive to damage from superficial siderosis caused by the breakdown of slow or repeated episodes of subarachnoid hemorrhage into hemosiderin (Fig 13). It is postulated that the sensitivity of cranial nerve VIII to subpial hemosiderin deposition is due to its long cisternal segment, which exposes it to a high concentration of iron, in combination with the fact that the transition from central to peripheral myelin occurs near the IAC in cranial nerve VIII but relatively close to the brainstem in cranial nerves III–XII. The central myelin and the microglia that produce it are especially sensitive to siderosis. The high iron concentration lining the brain and cranial nerves will cause local magnetic inhomogeneity and is most easily visualized on susceptibility-weighted or gradient-echo T2*-weighted images (15,16).

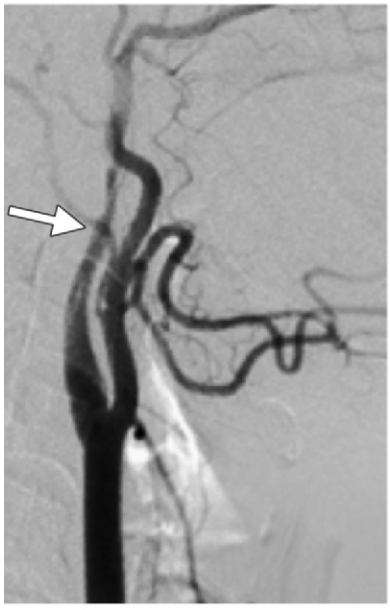
Sympathetic Innervation of the Globe

Sympathetic innervation of the globe is separate from the cranial nerves and visual reflex pathways. However, familiarity with the anatomy of this pathway is important, since a patient with the clinical picture of oculosympathetic paresis (Horner syndrome) may have any one of a variety of conditions, which range from mild to life threatening (Fig 14) (17,18). Sympathetic innervation of the globe consists of three groups of neurons. The first-order neurons descend from the hypothalamus to the C8–T2 levels of the spinal cord, where they synapse with the second-order neurons, which travel from the sympathetic trunk to the superior cervical ganglion near the carotid bifurcation. These second-order neurons then synapse with the third-order (postganglionic) neurons, which ascend within the adventitia of the ICA through the cavernous sinus, join with V1, and travel to the orbit. Lesions that interrupt sympathetic innervation of the orbit lead to unopposed parasympathetic input to the pupil, resulting in pupillary constriction (miosis). The

Teaching Point



a. b.



c.

Figure 14. Horner syndrome in a 59-year-old woman who presented with headache. Axial fat-saturated T1-weighted MR image **(a)**, axial time-of-flight MR angiogram **(b)**, and digital subtraction angiogram **(c)** show a right internal carotid dissection (arrow) disrupting sympathetic input to the right eye. This finding was confirmed at diagnostic angiography. MR evaluation of carotid dissection is best performed with axial fat-saturated T1-weighted imaging and time-of-flight MR angiography.

sympathetic neurons also innervate the Müller muscle, which is responsible for a minor portion of upper eyelid elevation and lower eyelid retraction. Therefore, loss of sympathetic innervation will also cause ptosis due to Müller muscle paresis; however, the degree of ptosis seen in oculosympathetic paresis will be minor compared with that seen in a cranial nerve III lesion that denervates the levator palpebrae muscle (18).

Disruption can occur at any point along the sympathetic pathway. Central or first-order Horner syndrome is caused by a lesion in the hypothalamus, brainstem, or spinal cord that disrupts the first-order neurons (18), including infarction of the lateral medulla, in which Horner syndrome will be seen in conjunction with Wallenberg syndrome (19).

Preganglionic or second-order Horner syndrome is typically caused by lesions at the lung apex or thoracic outlet in adults (17), or by birth trauma in neonates (20). Children with no history of trauma who present with acquired Horner syndrome should be evaluated for neuroblastoma (20).

Postganglionic or third-order syndrome is often secondary to trauma to or surgery of the ICA or to lesions in the cavernous sinus (18).

In a large series of patients with Horner syndrome (as demonstrated with pupillography), the disease had an unknown cause in 40% of cases and was presumed to be secondary to vascular disease. Of the remaining cases, 13% were due to a central cause, 44% were preganglionic, and 43% were postganglionic (21).

The fibers responsible for facial sweating (except those that travel to the medial forehead) branch off at the superior cervical ganglion and travel with the external carotid artery; therefore, postganglionic lesions affecting the ICA or cavernous sinus lead to anhidrosis limited to the medial forehead, whereas first- and second-order Horner syndrome will cause anhidrosis of the entire face (22).

The associated findings will often help delineate lesion location in the pathway. Central Horner

syndrome is often accompanied by additional findings related to the causative lesion (eg, other neurologic findings in stroke, findings of mass effect from a central neoplasm) (22). Postganglionic Horner syndrome can be differentiated from central and preganglionic Horner syndrome with use of hydroxyamphetamine or dilute phenylephrine eyedrops, which cause release of norepinephrine from adrenergic nerve endings. If the causative lesion affects the third-order (postganglionic) neurons, the denervated pupil will be hypersensitive to the norepinephrine and will dilate to a greater extent than the unaffected pupil. Alternatively, if the lesion involves the central (preganglionic) neurons, the pupillary dilatation will be minimal or absent (23). Typically, the clinical findings are also used to help elucidate the cause, such as brachial plexus dysfunction from a superior sulcus tumor causing preganglionic Horner syndrome or associated dysfunction of cranial nerves III–VI in the case of a cavernous sinus lesion causing postganglionic Horner syndrome (18).

Visual Reflex Pathways

There are multiple reflex pathways that provide cortical input to the visual system to allow activities such as the smooth pursuit of an object across the visual field, saccades, consensual blinking in response to stimulation of a single cornea, and consensual pupillary constriction in response to light directed onto a single retina. Disruption of these pathways can manifest in a variety of ways. Correlation of clinical findings with dedicated neuroimaging findings can often provide a specific diagnosis, or at least a reasonable differential diagnosis.

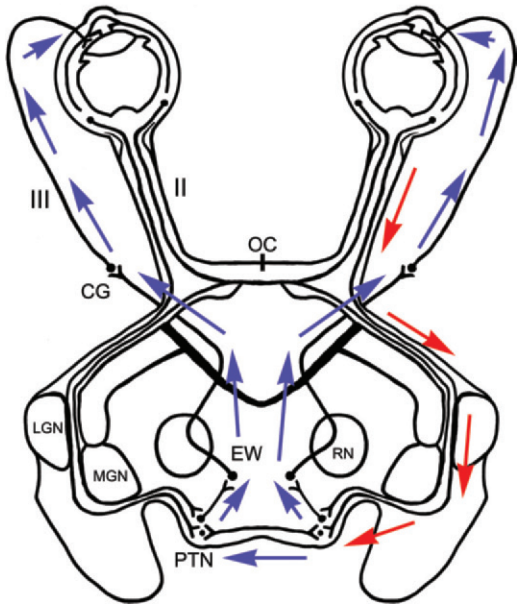


Figure 15. Drawing illustrates the pupillary light reflex. The afferent signal pathway (red arrows) relays the signal from the retina, along the optic nerve and optic radiations to the pretectal nucleus, where the efferent signal pathway (blue arrows) carries the signal to the Edinger-Westphal nuclei, leading to parasympathetic input on both pupils with resultant constriction. *CG* = ciliary ganglion, *EW* = Edinger-Westphal nucleus of cranial nerve III, *LGN* = lateral geniculate nucleus, *MGN* = medial geniculate nucleus, *OC* = optic chiasm, *PTN* = pretectal nucleus, *RN* = red nucleus, *III* = cranial nerve III, *II* = cranial nerve II. (Adapted, with permission, from reference 24.)

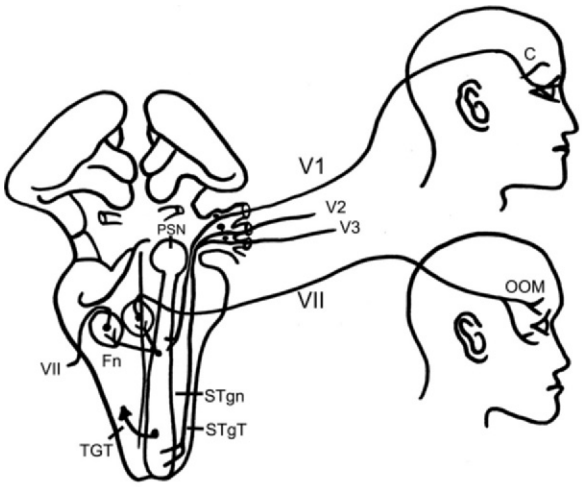
Light Reflexes

Afferent Pupillary Defect (Marcus Gunn Pupil)

Teaching Point

When light hits the retinal ganglion cells, the information is transmitted via the afferent pupillary pathway along the optic nerves to the optic chiasm, then along the optic tracts to synapse in the pretectal nucleus in the midbrain. From there, fibers are sent via the tectotegmental tract to both Edinger-Westphal nuclei, where the efferent pupillary pathway originates and sends parasympathetic input to both pupils via cranial nerve III, leading to pupillary constriction. If the afferent and efferent pathways are functioning properly, the pupils should react equally to light input on the retina, and there should be consensual pupillary constriction when light is directed into the contralateral eye (Fig 15) (3,24). The "swinging flashlight" test is used to stimulate each retina separately and to evaluate for a relative afferent pupillary defect (Marcus Gunn pupil) (25). Light shone into an eye with a relative afferent pupillary defect will result in decreased constriction of both pupils because the light is not effectively transmitted along the afferent pupillary pathway and therefore does not reach the Edinger-Westphal nuclei of cranial nerve III. A Marcus Gunn pupil is a nonspecific marker of partial optic nerve dysfunction.

The term *Argyll-Robertson pupil* refers to a small pupil that does not react to light but has intact accommodation (light-near dissociation). This condition has classically been associated with neurosyphilis but can also be seen with diabetes, multiple sclerosis, and midbrain neoplasms, among other causes (26). Argyll-Robertson pupil is caused by a dorsal midbrain lesion that disrupts the pupillary light reflex pathway



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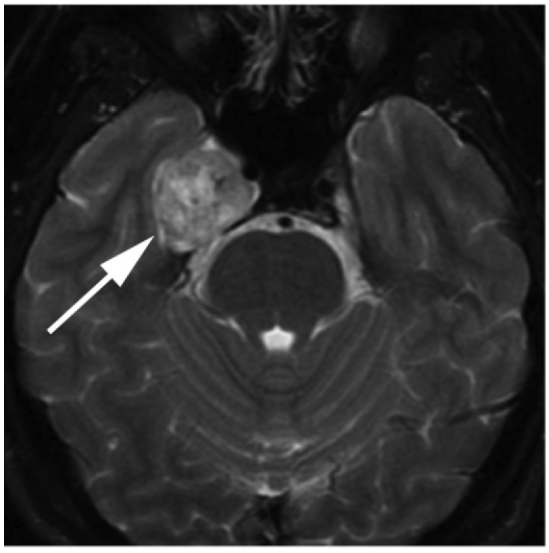

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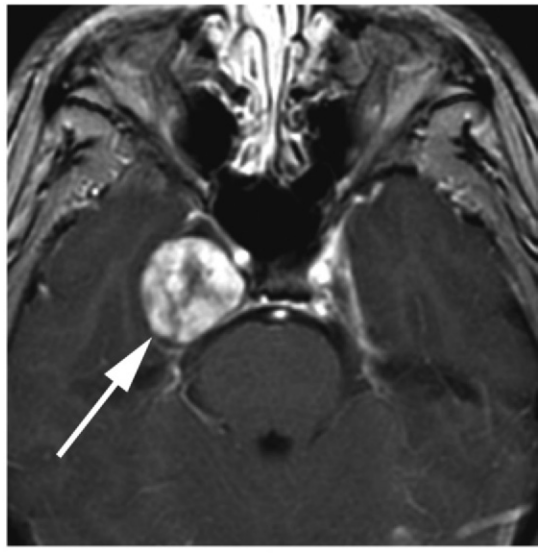

c.

Figure 16. **(a)** Drawing illustrates the corneal reflex. *C* = cornea, *V1* = ophthalmic division of cranial nerve V, *V2* = maxillary division of cranial nerve V, *V3* = mandibular division of cranial nerve V, *Fn* = facial nucleus, *OOM* = orbicularis oculi muscle, *PSN* = principal sensory nucleus of cranial nerve V, *VII* = cranial nerve VII, *STgn* = spinal trigeminal nucleus, *STgT* = spinal trigeminal tract, *TGT* = trigeminothalamic pain fiber. (Adapted, with permission, from reference 24.) **(b, c)** Schwannoma in a 38-year-old man with right facial numbness. Axial T2-weighted **(b)** and postcontrast T1-weighted **(c)** MR images demonstrate a schwannoma of the right trigeminal nerve (arrow) that disrupted the right corneal reflex.

but spares the more ventral pupillary accommodation reflex pathway (27).

Corneal Reflex

Stimulation of the cornea in one eye will normally cause blinking of both eyes, a consensual motor response. This is typically tested clinically with cotton applied to one cornea. The stimulation causes the ophthalmic division of the trigeminal nerve to send signals to the principal sensory nucleus of cranial nerve V, which sends axons to *both* cranial nerve VII motor nuclei, causing blinking of both eyes. A defect in cranial nerve V will lead to absence of blinking in both eyes when the affected eye is stimulated; a defect in cranial nerve VII will lead to absence of blinking in the ipsilateral eye (Fig 16) (28).

Internuclear Ophthalmoplegia

Tracking an object that is moving horizontally across the visual field requires firing of cranial nerve VI to control the lateral rectus muscle in one eye and of cranial nerve III to control the medial rectus muscle in the other eye. The concerted movements of lateral tracking are under the control of the frontal eye fields. The frontal eye fields send input to the paramedian pontine reticular formation, which in turn alerts cranial nerve VI to send a signal to activate the lateral rectus muscle. A signal is also sent from cranial nerve VI via the MLF to the contralateral cranial nerve III fibers responsible for medial rectus muscle activity to allow concerted eye movements (Fig 17). The MLF consists of paired white matter tracts that lie in the dorsomedial pontine and midbrain tegmentum near the midline (8). A defect in one MLF tract will prevent the signal from cranial nerve VI from reaching cranial nerve III, leading to a disorder in lateral conjugate gaze with weak adduction in the ipsilateral eye and nystagmus of the abducting eye, a condition known as INO (29). Convergence and

Teaching Point

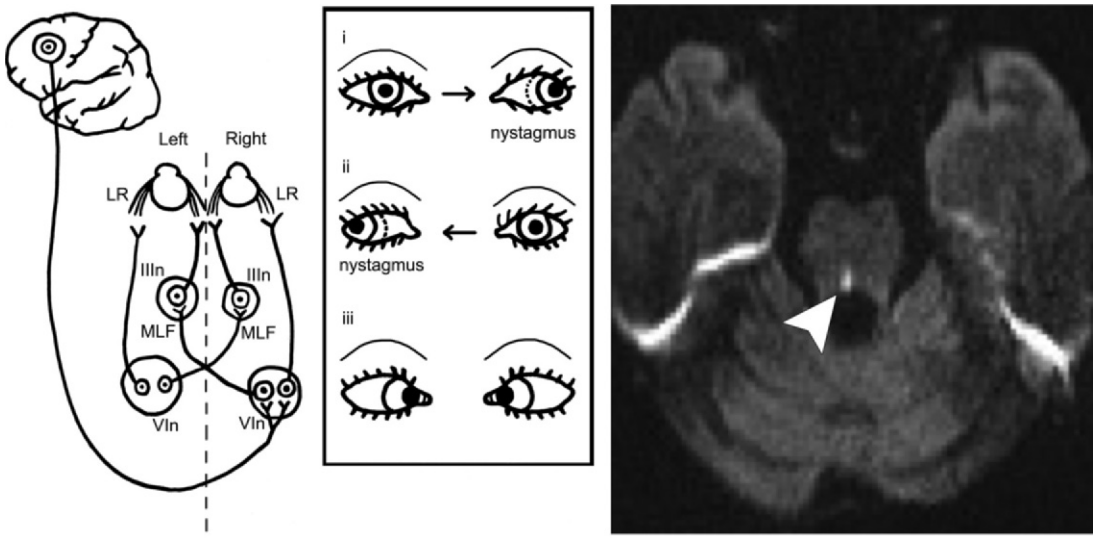

Figure 17. **(a)** Drawing illustrates bilateral internuclear ophthalmoplegia (INO). On lateral gaze, the patient will demonstrate nystagmus of the abducting eye (*i* and *ii*), but convergence will be spared *(iii)*. *LR* = lateral rectus muscle, *VIn* = cranial nerve VI nucleus, *IIIn* = cranial nerve III nucleus. (Adapted, with permission, from reference 24.) **(b)** Acute infarct in a 66-year-old man with a 3-day history of double vision. At physical examination, when the patient was asked to look to the left, weak adduction of the right eye and horizontal nystagmus of the left eye were noted. Convergence and accommodation were spared. Axial diffusion-weighted MR image shows an acute infarct of the right MLF tract (arrowhead), resulting in INO and double vision.

accommodation are intact in isolated INO, since the nuclei innervating the medial rectus muscles and parasympathetic fibers are unaffected by lesions in the MLF (28). INO is one of the most specifically localized lesions in the brain (30). It has many causes, the most common of which are demyelinating diseases such as multiple sclerosis and brainstem infarction (31).

The MLF tracts are in proximity to each other, and bilateral injury is common (32). Patients with injury to both MLF tracts will present with walleyed bilateral INO syndrome, which is characterized by exotropia in primary gaze position (walleye) and bilateral INO (33). More extensive injury in the dorsal pontine tegmentum (usually secondary to infarct) will result in damage to the paramedian pontine reticular formation and abducens nucleus in addition to the MLF, leading to "one-and-a-half syndrome," which is characterized by lateral gaze palsy when the patient directs the gaze toward the affected side and INO when the patient looks to the opposite side (34).

Horizontal and Vertical Gaze

There are separate brain centers that control horizontal and vertical gaze. These centers receive input from the cortical eye fields (frontal, parietal, and supplementary), as well as the vestibular, smooth pursuit, and saccadic systems; however, all these systems act through a common final pathway, which is distinct for the horizontal and vertical gaze centers (35).

The horizontal gaze centers lie in the pontine tegmentum, and, as mentioned earlier, the common final pathways for the numerous inputs controlling horizontal eye movements are the paramedian pontine reticular formation, the nuclei of cranial nerves III and VI, and the MLF (36). The vertical gaze centers are located in the midbrain and include *(a)* the rostral interstitial nucleus of the MLF, which controls vertical and torsional saccades, and *(b)* the interstitial nucleus of Cajal, which serves as the neuronal integrator (37). The inputs to vertical gaze act through the final common pathway of the nuclei of cranial nerves III and IV (38).

Numerous disease entities can impact the vertical gaze center, including progressive supranuclear palsy, which is a neurodegenerative disease related to τ protein deposition. There are several variants of this disease, but the classic phenotype consists of parkinsonism, supranuclear gaze palsy, and postural instability. Impairment of downward gaze is the most specific ocular disease, but paralysis of upward and horizontal gaze can also be seen. There are no specific imaging findings in progressive supranuclear palsy, but atrophy of

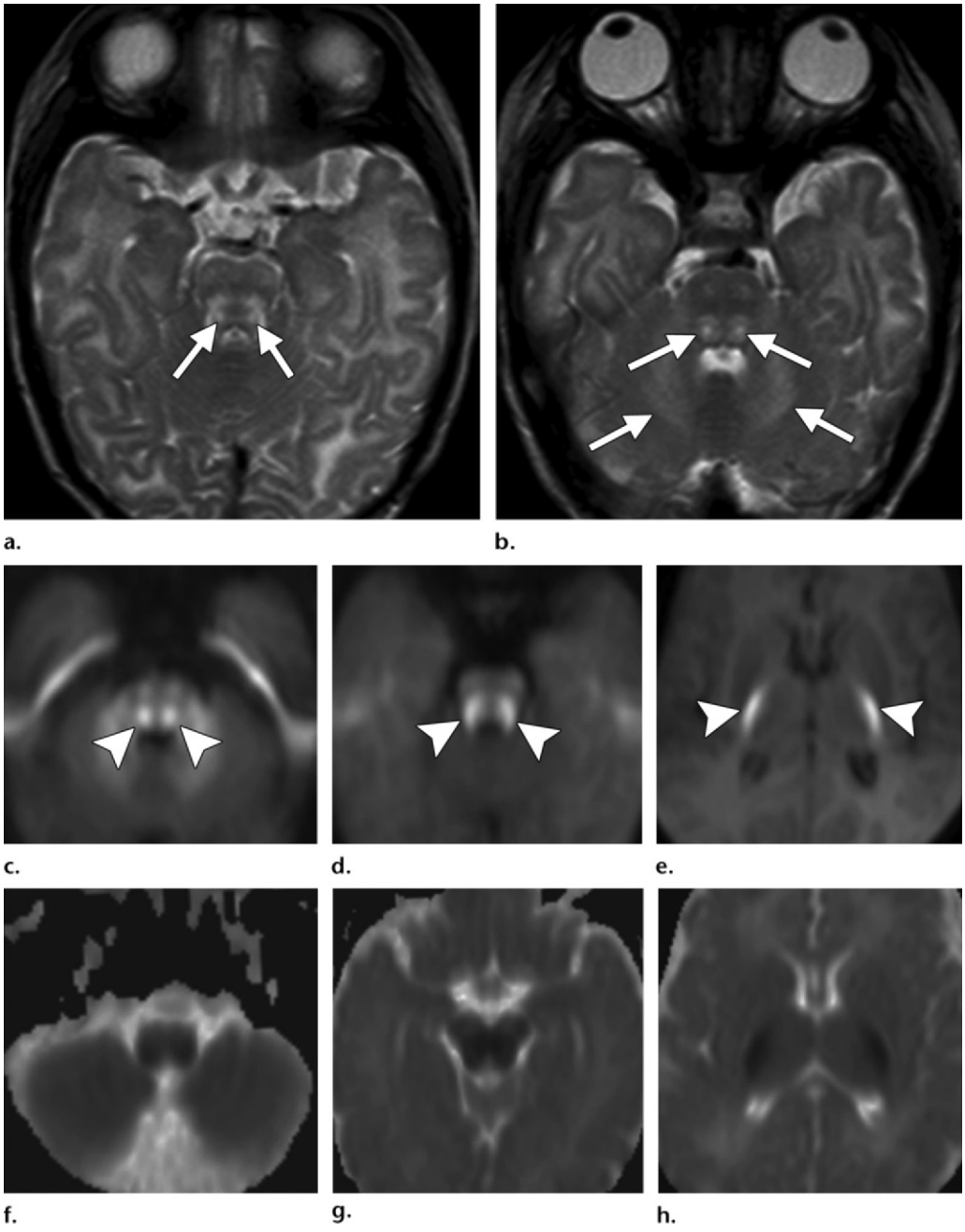

Figure 18. Maple syrup urine disease in a 7-day-old male neonate who presented with increasing irritability and dysconjugate gaze. **(a, b)** Axial T2-weighted MR images demonstrate diffuse T2 hyperintensity in the brainstem and cerebellum (arrows). **(c–h)** Axial diffusion-weighted MR images **(c–e)** and corresponding apparent diffusion coefficient maps **(f–h)** demonstrate restricted diffusion in the brainstem (arrowheads in **c** and **d**) and internal capsule (arrowheads in **e**). Maple syrup urine disease is an inherited disorder that prevents metabolism of branched chain amino acids, with resultant cerebral edema.

the rostral midbrain ("hummingbird sign") has been described on sagittal images (39). Dorsal midbrain (Parinaud) syndrome also has a characteristic spectrum of findings, including limitation of all upward eye movements (saccades, smooth pursuit, and vestibulo-ocular reflex). This syndrome has a number of causes, including pineal tumors, germinomas, multiple sclerosis, infarcts, and hydrocephalus, among many others (35).

The extensive input to the vertical and horizontal gaze centers makes these final common pathways susceptible to a variety of diseases that affect the central nervous system. Metabolic, infectious, toxic, and demyelinating diseases can impact any of the visual reflex pathways, manifesting as a horizontal or vertical gaze palsy (Fig 18) (40).

Conclusion

The visual system is complex and requires a great deal of cortical control to function properly. A variety of pathologic entities can impact the visual system, by disrupting either *(a)* the cranial nerves responsible for control of the globes, *(b)* the autonomic input to the globes, or *(c)* the reflex pathways, all of which allow the globes to function in concert. In a patient with visual problems, history and physical examination are invaluable in directing the clinician toward the appropriate therapy; they are also invaluable to the radiologist in guiding neuroimaging. For example, a patient with preganglionic oculosympathetic paresis will require imaging of the cervicothoracic spine, lung apices, and neck in addition to imaging of the brain, whereas a patient with postganglionic oculosympathetic paresis will most likely require imaging of the carotid arteries and cavernous sinuses. Knowledge of the anatomy and function of the visual system will allow the radiologist to tailor the imaging study appropriately and to be cognizant of the myriad intracranial diseases that may lead to ophthalmoplegia, which will facilitate improved confidence and more precise diagnosis in these difficult cases.

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Intracranial Causes of Ophthalmoplegia: The Visual Reflex Pathways

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A variety of pathologic conditions can affect cranial nerve III. Its close association with the posterior cerebral and superior cerebellar arteries makes cranial nerve III susceptible to compression by vascular lesions such as posterior communicating artery aneurysms. The location of the nerve as it courses over the petroclinoid ligament also makes it susceptible to compression during herniation of the uncus through the tentorium cerebelli.

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The cisternal portion of cranial nerve VI exits the brainstem near the midline through the space between the pons and the pyramid of the medulla oblongata. The nerve courses anteriorly in the prepontine cistern and penetrates the dura mater to enter the Dorello canal and then the cavernous sinus, where it is the only nerve to travel within the venous sinusoids of the cavernous sinus (cranial nerves III, IV, V1, and V2 all lie within the lateral dural wall of the cavernous sinus).

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Sympathetic innervation of the globe consists of three groups of neurons. The first-order neurons descend from the hypothalamus to the C8–T2 levels of the spinal cord, where they synapse with the second-order neurons, which travel from the sympathetic trunk to the superior cervical ganglion near the carotid bifurcation. These second-order neurons then synapse with the third-order (postganglionic) neurons, which ascend within the adventitia of the ICA through the cavernous sinus, join with V1, and travel to the orbit.

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When light hits the retinal ganglion cells, the information is transmitted via the afferent pupillary pathway along the optic nerves to the optic chiasm, then along the optic tracts to synapse in the pretectal nucleus in the midbrain. From there, fibers are sent via the tectotegmental tract to both Edinger-Westphal nuclei, where the efferent pupillary pathway originates and sends parasympathetic input to both pupils via cranial nerve III, leading to pupillary constriction. If the afferent and efferent pathways are functioning properly, the pupils should react equally to light input on the retina, and there should be consensual pupillary constriction when light is directed into the contralateral eye.

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The concerted movements of lateral tracking are under the control of the frontal eye fields. The frontal eye fields send input to the paramedian pontine reticular formation, which in turn alerts cranial nerve VI to send a signal to activate the lateral rectus muscle. A signal is also sent from cranial nerve VI via the MLF to the contralateral cranial nerve III fibers responsible for medial rectus muscle activity to allow concerted eye movements. The MLF consists of paired white matter tracts that lie in the dorsomedial pontine and midbrain tegmentum near the midline. A defect in one MLF tract will prevent the signal from cranial nerve VI from reaching cranial nerve III, leading to a disorder in lateral conjugate gaze with weak adduction in the ipsilateral eye and nystagmus of the abducting eye, a condition known as INO.