Paralytic Strabismus: Third, Fourth, and Sixth Nerve Palsy

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KEYWORDS
- Paralytic strabismus • Nerve palsy • Ocular motor nerves
- Eye movement abnormalities

ANATOMY

Eye movements are subserved by the ocular motor nerves (cranial nerves 3, 4, and 6), which innervate the 6 extraocular muscles of each eye (**Fig. 1**). The oculomotor (third) nerve innervates the medial rectus, inferior rectus, superior rectus, and inferior oblique muscles, as well as the levator palpebrae. The trochlear (fourth) nerve innervates the superior oblique muscle, and the abducens (sixth) nerve innervates the lateral rectus muscle.

The nuclear complex of the third nerve lies in the dorsal midbrain, anterior to the cerebral aqueduct. It consists of multiple subnuclei that give rise to distinct sets of fibers destined for the muscles targeted by the third nerve. In general, the axons arising from these subnuclei travel in the ipsilateral nerve, except axons arising from the superior rectus subnucleus that travel through the contralateral third nerve complex to join the third nerve on that side.[1] In addition, a single central caudate nucleus issues fibers that join both third nerves to innervate the levator palpebrae muscles bilaterally.[2] The preganglionic cholinergic fibers that innervate the pupillary constrictor arise from the paired Edinger-Westphal nuclei. On exiting the nuclear complex, the third nerve fascicles travel ventrally, traversing the red nucleus and the cerebral peduncles, before exiting the midbrain into the interpeduncular fossa. The proximal portion of the nerve passes between the superior cerebellar and posterior cerebral arteries.[3] The axons are topographically arranged, with fibers for the inferior rectus, medial rectus, superior rectus, and inferior oblique arranged along the

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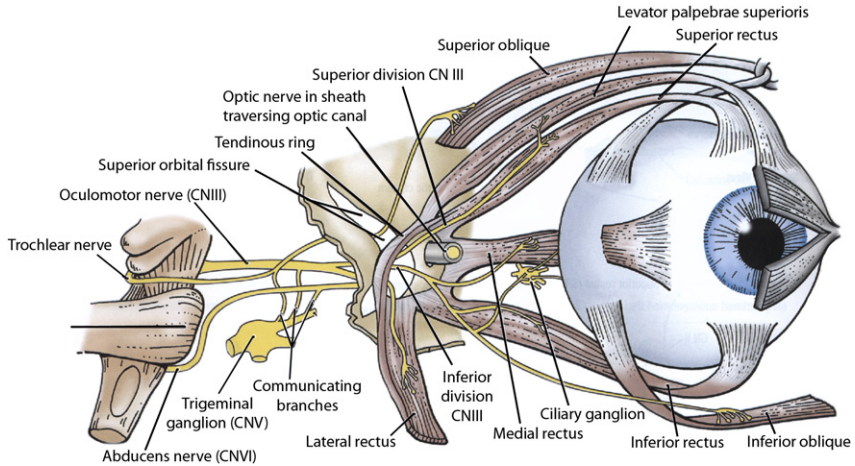
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Fig. 1. Anatomic structures subserving eye movements: lateral view of the right eye. The oculomotor nerve (CN III), trochlear nerve (CN IV), and abducens nerve (CN VI) arise from the brainstem. After passing through the subarachnoid space and cavernous sinus, they enter the orbit through the superior orbital fissure. The oculomotor nerve divides into superior and inferior divisions, and ultimately innervates the superior rectus, inferior rectus, medial rectus, inferior oblique (shown cut), and levator palpebrae muscles. In addition, parasympathetic fibers of the third nerve synapse in the ciliary ganglion then innervate the pupillary constrictor muscle. The trochlear nerve innervates the superior oblique muscle. The abducens nerve innervates the lateral rectus muscle (shown cut). (*Adapted from* Agur AMR, Dalley AF. Grant's atlas of anatomy. 12th edition. Philadelphia: Lippincott, Williams & Wilkins; 2009; with permission.)

medial-to-lateral axis. Pupillary fibers are generally located superficially, in the superior and medial portion of the nerve.

The trochlear (fourth) nucleus is situated in the pontomesencephalic junction, ventral to the cerebral aqueduct. Unlike all other cranial nerves, these axons exit the brainstem dorsally. They then decussate within the anterior medullary velum (beneath the inferior colliculi), and ultimately innervate the contralateral superior oblique muscle.

The abducens (sixth) nucleus lies in the dorsal pons, in close proximity to the facial (seventh) nerve fascicle. The sixth nerve fascicle travels ventrally, through the corticospinal tracts, before exiting anterolaterally at the pontomedullary junction.

The 3 ocular motor nerves pass through the subarachnoid space before piercing the dura and arriving at the cavernous sinus (**Fig. 2**). Although the third and fourth nerves are situated along the lateral wall of the cavernous sinus, the abducens nerve has a more medial position, just lateral to the internal carotid artery. The third nerve splits into superior and inferior divisions within the anterior cavernous sinus. The superior division innervates the levator palpebrae and the superior rectus muscles, whereas the inferior division innervates the remaining third nerve muscles (the medial rectus, inferior rectus, inferior oblique, and the pupillary constrictor). All 3 ocular motor nerves exit the cavernous sinus via the superior orbital fissure, and then pass through the orbital apex to reach their target muscles.

The blood supply to the third, fourth, and sixth nerves has multiple sources that feed a vasa nervorum capillary network.[4] In the subarachnoid space, the third nerve is supplied by small thalamomesenchephalic branches from the basilar artery and posterior ciliary artery (PCA); in the cavernous sinus, it is supplied by branches of
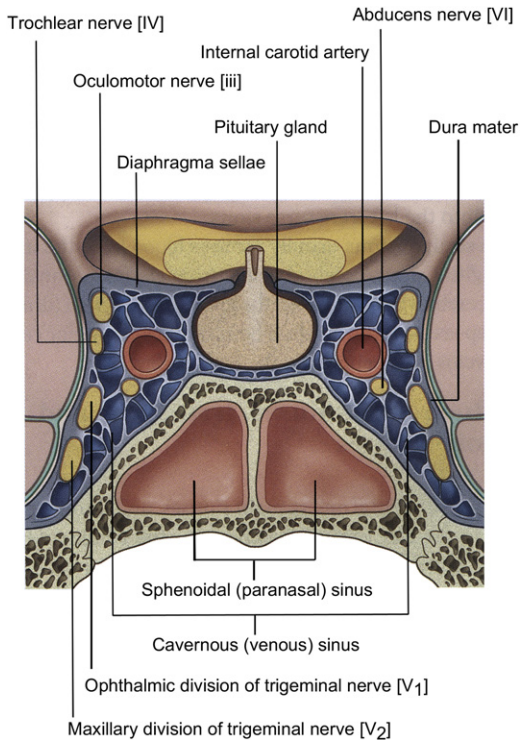
Trochlear nerve [IV]

Abducens nerve [VI]

Internal carotid artery

Oculomotor nerve [iii]

Pituitary gland

Dura mater

Diaphragma sellae

Sphenoidal (paranasal) sinus

Cavernous (venous) sinus

Ophthalmic division of trigeminal nerve [V$_1$]

Maxillary division of trigeminal nerve [V$_2$]

Fig. 2. The cavernous sinus, coronal view. The oculomotor nerve and trochlear nerve are situated on the lateral wall of the cavernous sinus (along with the ophthalmic and maxillary divisions of the trigeminal nerve). The abducens nerve floats freely within the cavernous sinus. The internal carotid artery is located medially in the cavernous sinus, and the pituitary gland is within the sella turcica in the midline. (*Reprinted from* Drake R, Vogl W, Mitchell A. Gray's anatomy for students. 2nd edition. London: Churchill Livingstone; 2010; with permission.)

the intracavernous carotid, and within the orbit its supply arises from recurrent branches of the ophthalmic artery. A watershed zone may exist between the subarachnoid and intracavernous portions of this blood supply.[5] In the subarachnoid segment, the blood supply of the fourth nerve comprises branches from the superior cerebellar artery (SCA), and that of the sixth nerve arises from branches of the PCA and SCA.[4] In the cavernous sinus and the orbit, the blood supply to both of these nerves arises from the same vessels that supply the third nerve.

THIRD NERVE PALSY
Clinical Features

Complete, isolated third nerve palsy causes ipsilateral weakness of elevation, depression, and adduction of the globe, in combination with ptosis and mydriasis. Depending on the specific cause, complete third nerve palsy may involve the pupil (causing mydriasis) or spare the pupil (**Figs. 3** and **4**). In partial third nerve palsy, different patterns of impaired motility may occur with or without pupillary involvement. The motility deficit may be subtle, and a reduced duction may not be easily observed. In this case, more detailed assessment of alignment, with alternate cover or Maddox rod testing, will
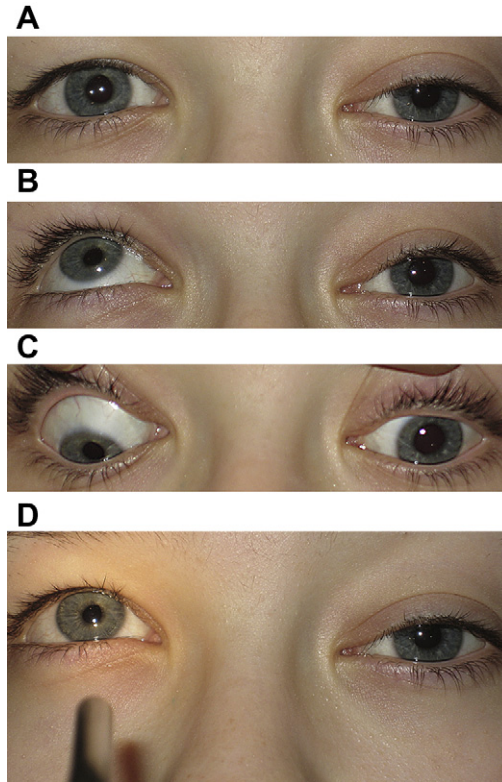
Fig. 3. A 32-year-old woman with traumatic complete left third nerve palsy, showing right hypertropia in upgaze that becomes left hypertropia in downgaze. (*A*) Left ptosis, mydriasis, exotropia, and right hypertropia in primary gaze. (*B*) Absent left elevation. (*C*) Reduced left depression. (*D*) The left pupil shows minimal consensual response to light, with greater anisocoria.

show an incomitant pattern of ocular misalignment supporting the diagnosis of partial third nerve palsy. A characteristic feature is that the affected eye is hypotropic in upgaze but hypertropic in downgaze, because of the combined weakness of the superior and inferior rectus muscles.

As opposed to lesions of the third nerve fascicle or nerve, a lesion of the third nerve nucleus will cause bilateral abnormalities. Specifically, there is bilateral ptosis (because the central caudal nucleus supplies both levator palpebrae muscles) and a bilateral elevation deficit (because the superior rectus subnucleus sends fibers through the contralateral third nerve nucleus to join the opposite nerve) (**Fig. 5**).[1,6,7] Therefore, the classic clinical picture of unilateral nuclear third nerve palsy is ipsilateral mydriasis; ipsilateral weakness of the medial rectus, inferior rectus, and inferior oblique muscles; bilateral ptosis; and bilateral superior rectus weakness.

As the third nerve fascicle travels ventrally through the midbrain, it is vulnerable to an intraparenchymal lesion. Partial deficits are possible, in keeping with the topographic arrangement of fibers within the nerve fascicle.[2,8–10] In these cases, other neurologic deficits often accompany the third nerve palsy. For example, a lesion also affecting the corticospinal tracts in the cerebral peduncle will cause contralateral hemiparesis (Weber syndrome), a lesion involving the red nucleus will cause contralateral limb
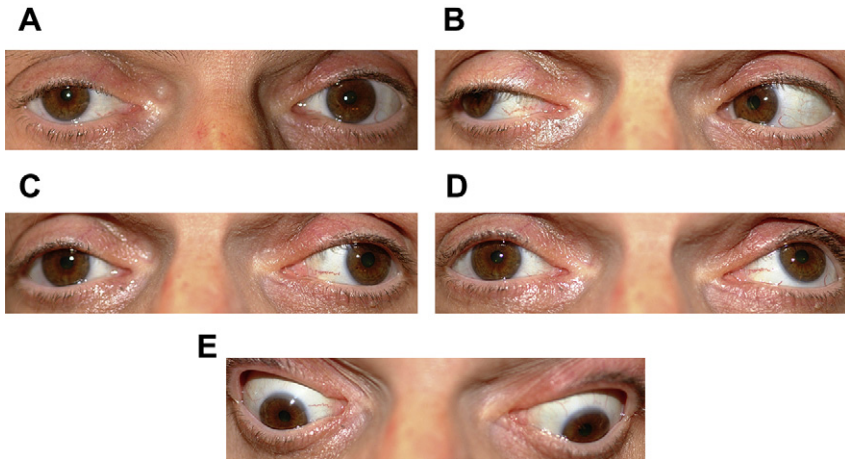
Fig. 4. A 55-year-old woman with a microvasculopathic partial right third nerve palsy due to diabetes and hypertension. Magnetic resonance imaging and magnetic resonance angiography were normal. (*A*) Right ptosis without mydriasis in primary position. Mild physiologic anisocoria was present. (*B*) Normal right gaze. (*C*) Decreased right adduction on left gaze. (*D*) Decreased right elevation on upgaze. (*E*) Decreased right depression on downgaze. The motility became normal within 8 weeks.

tremor (Benedikt syndrome), and a lesion involving the brachium conjunctivum (involving the crossing dentatorubrothalamic fibers of the superior cerebellar peduncle) will cause contralateral ataxia (Claude syndrome).[11] Rarely, fascicular third nerve palsy may occur in isolation.[6]

Given the segregation of the third nerve into superior and inferior divisions, a lesion of the anterior cavernous sinus or orbit may cause selective impairments. Disruption of the superior division causes ptosis and impaired elevation, whereas disruption of the inferior division causes impaired depression, adduction, and mydriasis (**Figs. 6** and **7**).[12] However, in rare cases, more proximal lesions (ie, intraparenchymal fascicular lesions or subarachnoid lesions) may mimic a divisional palsy.[10,13–16]

Aberrant regeneration refers to miswiring of third nerve innervated structures, leading to patterns of co-contraction (ie, synkinesis).[17] Common manifestations are contraction of the levator palpebrae on adduction or depression of the eye, or miosis of a dilated pupil during adduction (**Fig. 8**). This phenomenon occurs in primary and secondary forms. Primary aberrant regeneration suggests chronic compression, typically due to an expanding cavernous sinus lesion such as a meningioma, aneurysm, tumor, or other mass.[18–20] Secondary aberrant regeneration occurs in the recovery phase following acute third nerve palsy, commonly after trauma but also after ophthalmoplegic migraine, pituitary apoplexy, or inflammation. Aberrant regeneration does not occur after vasculopathic third nerve palsy.

Differential Diagnosis

Nuclear or fascicular third nerve palsy is typically due to midbrain infarction from occlusion of a small penetrating artery from the proximal PCA. Other possible causes of midbrain disease include tumors, vascular malformations, abscesses, demyelination, and inflammatory disorders.

In the subarachnoid space, an expanding aneurysm of the posterior communicating artery (PComm) is an important cause of third nerve palsy. More than 90% of patients
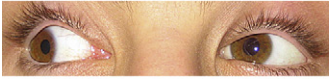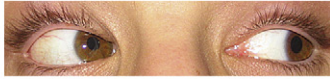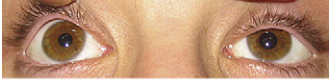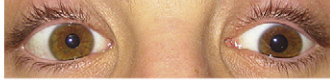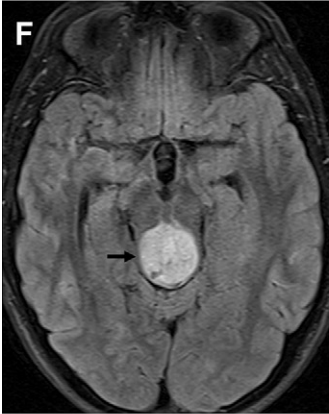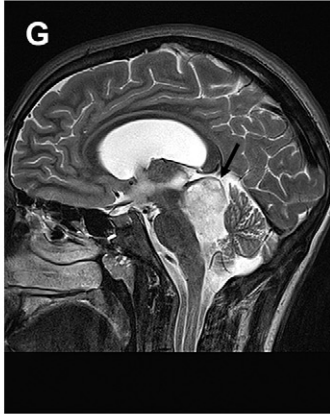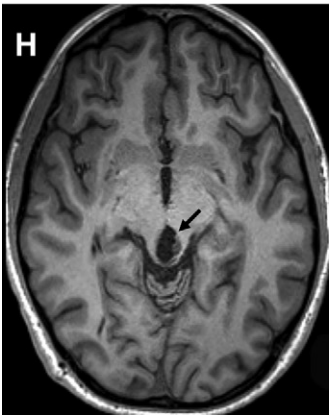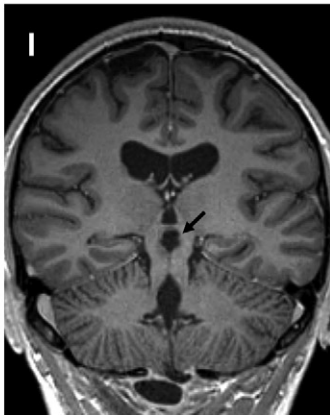
with subarachnoid hemorrhage from a PComm aneurysm initially present with a third nerve palsy.[21,22] These aneurysms commonly project posterolaterally to compress the third nerve and involve the pupillary fibers in most cases. When the motility deficits are complete, pupillary involvement is virtually always present. If the motility deficit is partial, then the pupil may initially be spared.[23] Sparing of pupillomotor fibers may occur because they are resistant to evenly distributed compression, or because they are positioned dorsally, and in some cases compression is limited to the inferior aspect of the nerve.[24] A PComm aneurysm presenting acutely as a third nerve palsy represents a true neurosurgical emergency and may be treated by surgical clipping or endovascular coiling.[25]

Microvascular third nerve palsy is commonly associated with risk factors including hypertension, diabetes, hyperlipidemia, advanced age, and smoking (see **Fig. 4**). This disorder results from impairment of microcirculation leading to circumscribed, ischemic demyelination of axons at the core of the nerve, typically in the cavernous sinus portion where a watershed territory exists.[5,26] Most of these patients exhibit pupillary sparing, because the pupillary fibers are located peripherally, closest to the blood supply provided by the surrounding vasa nervorum. However, some pupillary involvement may occur, typically with less than 1 mm (up to a maximum of 2.5 mm) of anisocoria found in approximately 40% of cases.[27] A microvascular third nerve palsy is frequently associated with orbital pain, which can be severe. Although it remains uncertain, the pain may result from ischemia of trigeminal sensory fibers that join the third nerve within the cavernous sinus.[28] There is an excellent prognosis for recovery of motility deficits from microvascular third nerve palsy, typically in 8 to 12 weeks.[29]

Severe trauma is another common cause of third nerve palsies, involving traction at the skull base or fracture of the bones of the orbit or skull base (**Fig. 9**).[30,31] A third nerve palsy that follows minor head trauma may indicate an underlying structural lesion.[32,33] Although there is good prognosis for recovery following traumatic third nerve palsy, there is a high incidence of secondary aberrant regeneration.

Slowly progressive third nerve palsies occasionally occur due to growth of a primary tumor of the nerve or nerve sheath. These lesions include neurinomas, neurofibromas, neurilemmomas, and schwannomas.[34] Neuroimaging will identify an enlarged, enhancing nerve in these cases. Uncommonly, a malignant meningioma, glioblastoma multiforme, or lymphoma may directly affect the third nerve.[35]

Uncal herniation can cause direct compression of the third nerve against the free edge of the tentorium. In addition to third nerve deficits, these patients will have depressed mental status among other prominent neurologic deficits. In this situation, isolated pupil dilation may be the earliest manifestation of third nerve dysfunction. However, an isolated dilated pupil is never a manifestation of third nerve dysfunction in an awake and alert patient.

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Fig. 5. A 15-year-old boy with bilateral nuclear third nerve palsies following resection of a midline juvenile pilocytic astrocytoma. (*A*) Severe bilateral ptosis in primary gaze. Note compensatory contraction of the frontalis muscle. (*B*) Reduced left adduction. Mydriasis of the left pupil is observed. (*C*) Slightly reduced right adduction. (*D*) Severe elevation limitation on attempted upgaze. The vertical gaze limitation was not overcome by the oculocephalic maneuver. (*E*) Bilateral depression deficit, greater on the right than on the left. Preoperative axial fluid-attenuated inversion-recovery (FLAIR) (*F*) and sagittal T2-weighted brain MRI (*G*) revealed a large heterogeneous midline mass (*arrow*) compressing the dorsal midbrain and causing hydrocephalus. Axial (*H*) and coronal MRI (*I*) 2 years following surgical resection showing focal volume loss in the dorsal midbrain (*arrow*).
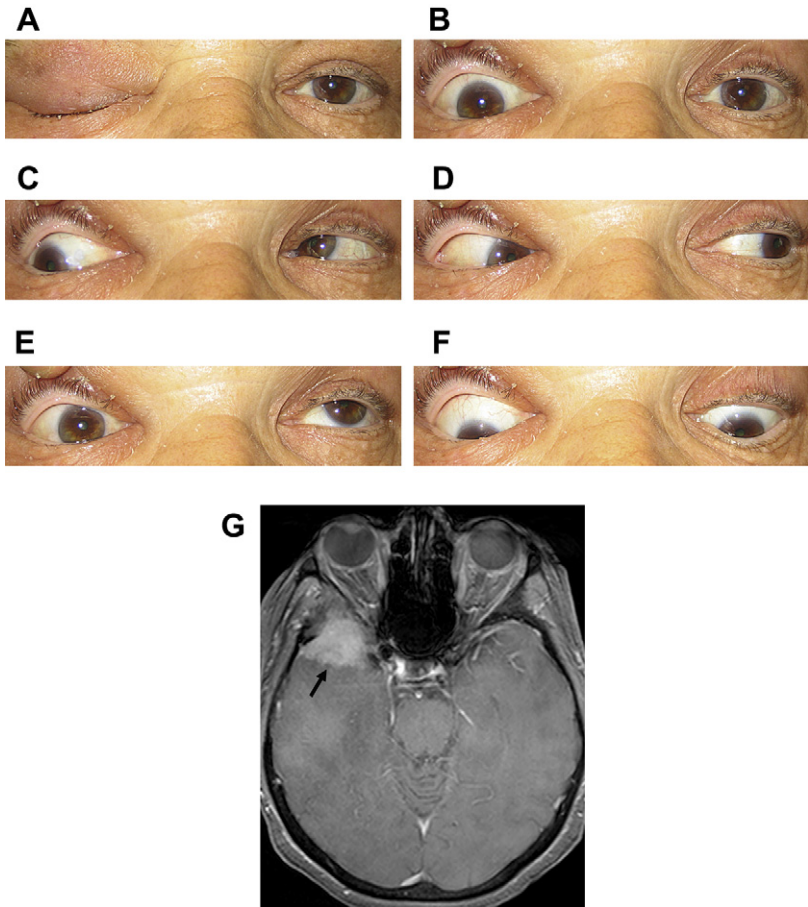
Fig. 6. 63-year-old woman with right superior divisional third nerve palsy following resection of right sphenoid wing meningioma, causing isolated dysfunction of the levator palpebrae and superior rectus muscles. (*A*) Complete right ptosis. (*B*) Slight right hypotropia in primary gaze. (*C*) Right hypotropia in right gaze. (*D*) Slight right hypotropia in left gaze. (*E*) Markedly reduced elevation of the right eye. (*F*) Normal downgaze. (*G*) Preoperative postcontrast T1-weighted brain MRI showing right sphenoid wing meningioma (*arrow*).

In the pediatric population, ophthalmoplegic migraine may cause transient isolated third nerve palsy. This rare form of complicated migraine typically presents before the age of 10 years.[36] Ipsilateral headache and nausea often accompany abnormal eye movements. For unclear reasons, third nerve involvement is most common, occurring in 95% of cases. The cause may relate to transient ischemia or compression of the nerve within the cavernous sinus by an edematous, dilated carotid artery.[37,38] This condition is a diagnosis of exclusion, after a workup including imaging, blood work, and often lumbar puncture are unrevealing. Ophthalmoplegic migraine should be considered extremely unlikely in an adult without prior history of similar episodes in childhood.

Isolated persistent third nerve palsy in childhood is commonly a congenital defect.[39] These cases are believed to result from aplasia or maldevelopment of the structures of the ocular motor nucleus due to in utero insult.[40] The motility deficit and ptosis is
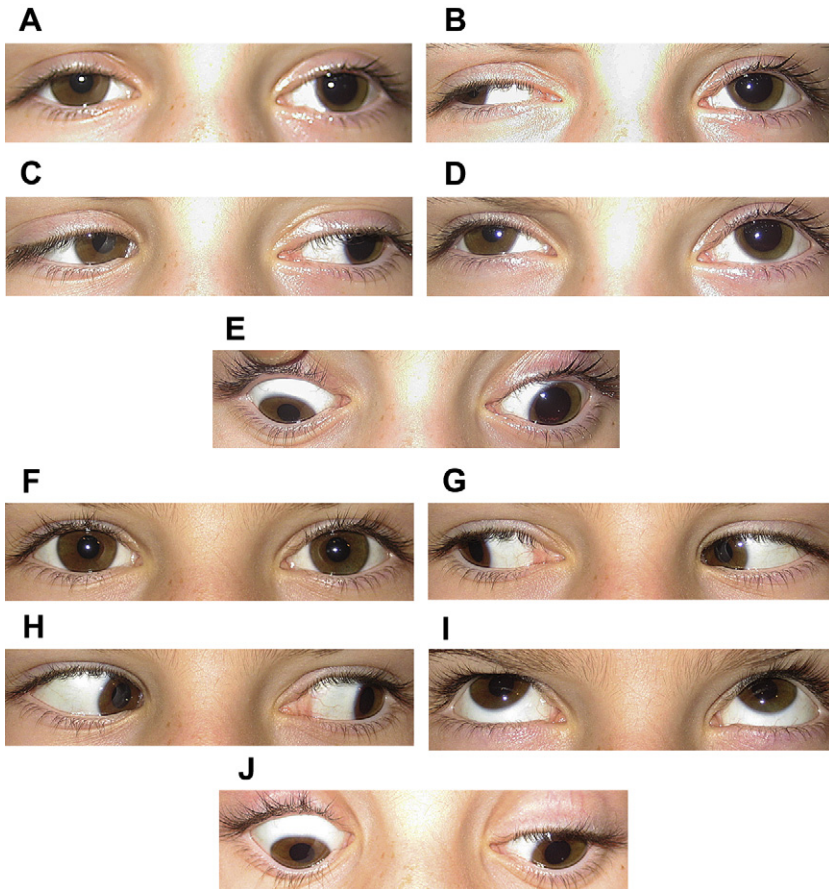
Fig. 7. An 8-year-old girl with idiopathic postviral left inferior divisional third nerve palsy, causing isolated dysfunction of the medial rectus, inferior rectus, and pupillary constrictor muscles. Brain MRI and spinal fluid constituents were normal. (*A*) Left mydriasis and exotropia. (*B*) Complete left adduction deficit on right gaze. (*C*) Normal left gaze. (*D*) Normal upgaze bilaterally (not fully seen in this photograph). (*E*) Left depression deficit. (*F*) At 3-month follow-up, there was marked improvement of the motility deficit, with residual left mydriasis (anisocoria greatest in light). (*G*) Left adduction deficit has resolved. (*H*) Left gaze remains normal. (*I*) Upgaze remains normal. (*J*) Slight left depression deficit persists.

typically accompanied by miosis, rather than mydriasis, which probably results from anomalous innervation of the pupillary constrictor. Cyclic oculomotor spasms may occur, which are characterized by brief (10–30 seconds), involuntary contractions of third nerve innervated structures, causing periods of adduction, lid elevation, and miosis.[41] This condition rarely occurs with acquired third nerve palsy, typically due to a compressive lesion.

Third nerve palsy frequently occurs in combination with other cranial nerve deficits. The disorders capable of affecting multiple cranial nerves include cavernous sinus lesions, neoplasms of the base of the skull, carcinomatous meningitis, sinus mucoceles, infections, and inflammatory conditions. These conditions are discussed later in this article.
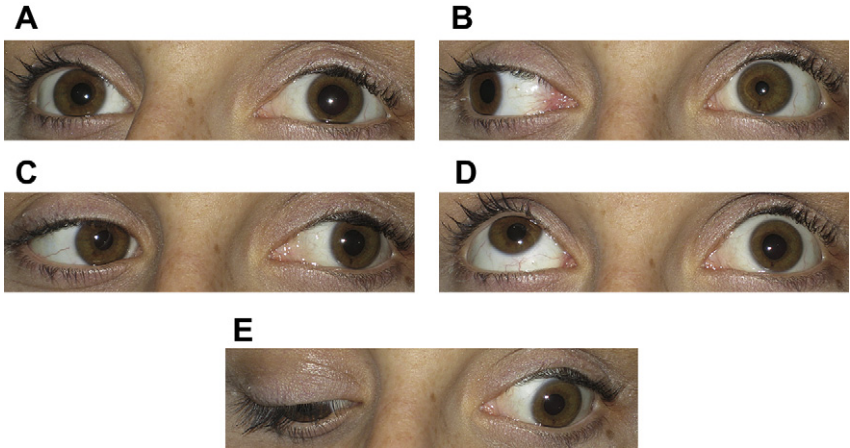
Fig. 8. A 45-year-old woman with aberrant regeneration following traumatic left third nerve palsy. (*A*) Left mydriasis, exotropia, and right hypertropia in primary position. (*B*) Reduced left adduction with synkinetic left pupillary constriction and left lid elevation. (*C*) Complete left gaze (not fully shown in this photograph). (*D*) Reduced left elevation. (*E*) Reduced left depression with abnormal lid elevation due to synkinesis.
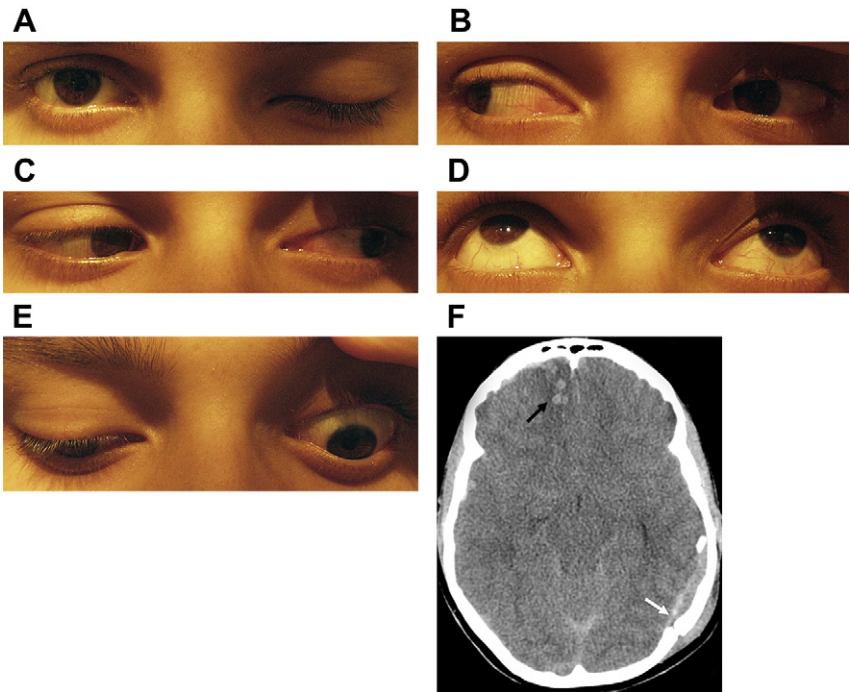
Fig. 9. A 14-year-old boy with left partial third nerve palsy following head trauma. (*A*) Complete left ptosis. (*B*) Reduced left adduction. No mydriasis is evident. (*C*) Complete left gaze. (*D*) Reduced left elevation. (*E*) Normal depression. (*F*) Noncontrast head computed tomography (CT) revealed frontal contusions (*black arrow*), occipital fracture, and epidural hematoma (*white arrow*). The motility deficit recovered completely within 3 months, without aberrant regeneration.

Diagnostic Testing

The appropriate workup for a patient with third nerve palsy depends on the patient's age and pupil function. In adults with acquired, isolated, complete, or partial third nerve palsy that involves the pupil, there is no controversy to the workup: these patients need urgent imaging to exclude a PComm aneurysm or other mass.[42,43] Computed tomography angiography (CTA) and magnetic resonance angiography are useful, but the exact sensitivity and availability of these tests vary across institutions.[44] Nevertheless, if these tests are negative, a catheter angiogram often remains necessary in these patients because small aneurysms are potentially missed on noninvasive imaging studies.

For patients with complete, pupil-sparing third nerve palsy who are more than 50 years of age and have vascular risk factors, clinical observation may be reasonable. If these patients fail to spontaneously recover within 12 weeks, then detailed neuroimaging is necessary. However, the appropriate threshold for obtaining imaging in this patient population remains an ongoing source of controversy. There are a growing number of reports of lesions diagnosed by magnetic resonance imaging (MRI) in patients who mimicked microvasculopathic third nerve palsy.[43] Therefore, in clinical practice it may be prudent to obtain imaging studies to exclude vascular lesions in these patients.

In patients with partial, pupil-sparing third nerve palsies, the threshold to obtain imaging is also low. Historically, it would have been reasonable to observe these patients for several days; in cases of evolving acute third nerve palsy due to aneurysm, mydriasis would occur in almost all cases within that time period.[23] If mydriasis develops, urgent imaging becomes necessary. If the motility deficit remains unaccompanied by pupillary abnormalities after 1 week, then a microvasculopathic cause is most likely. In the modern era, given the high risks of missing the diagnosis of an aneurysm and the increased availability of magnetic resonance (MR) or computed tomography (CT) imaging, it has become an appropriate strategy to obtain imaging in these patients earlier.

Consideration of imaging should also be given to patients with third nerve palsy due to trauma, especially if the extent of trauma was minor, because of the incidence of underlying mass lesions (including aneurysms). Imaging these patients will also evaluate for muscle entrapment due to fracture of the orbital wall.

In cases in which an infectious, inflammatory, or neoplastic cause is suspected, and MRI is negative or nonspecific, additional workup may include serologies for Lyme disease, syphilis, and an erythrocyte sedimentation rate to exclude temporal arteritis. Cerebrospinal fluid (CSF) analysis including cell counts, protein, glucose, cytology, and Lyme and Venereal Disease Reference Laboratory (VDRL) titers may be required.

Treatment

The treatment of diplopia due to acute third nerve palsy may include monocular patching or prisms. If the third nerve palsy is improving quickly over several weeks, prisms may be unnecessary and difficult to use successfully. If the misalignment remains fairly stable, then prisms may reduce diplopia in primary gaze. However, given the incomitance of these deviations, prisms are unlikely to alleviate diplopia in eccentric gaze, and patient satisfaction may vary.

Once ocular misalignment from third nerve palsy has been stable for 6 to 12 months, surgical correction can be considered. The complexity of these cases depends on whether the third nerve palsy is complete or partial. Complete third nerve palsy presents a highly incomitant deviation in the horizontal and vertical planes. The ultimate goal for surgery in these cases is to establish single binocular vision in the primary position.[45] Exodeviation in the primary position may be reduced by performing

a supramaximal lateral rectus recession (a weakening procedure that completely abolishes abduction), potentially in combination with a medial rectus resection (a tightening procedure to augment the muscle's action). A medial rectus resection alone often becomes ineffective in these cases. Other strategies include transposition of the horizontal muscles to facilitate vertical eye movements and transposition of the superior oblique tendon to create an adducting force.

For patients with partial third nerve palsy, the surgical plan is tailored to the specific pattern of misalignment. In general, a combination of procedures is used to achieve better alignment. These include resection of the partially paretic muscle and recession or posterior fixation suture of the contralateral yoke muscle. A posterior fixation suture creates a mild limitation of eye movement without affecting primary position. A recession procedure can be done with adjustable sutures so that the realignment can be fine-tuned based on the awake patient's subjective experience.[46] For instance, a patient with partial third nerve palsy causing isolated impairment of elevation or depression can be treated with a resection of the involved vertical muscle combined with an adjustable recession (or posterior fixation suture) of the contralateral yoke muscle, producing an improved field of single binocular vision.

The risks of surgery should be weighed carefully in the decision to treat patients with third nerve palsy. Patients should be warned that more disabling diplopia may occur following strabismus surgery, as the images from each eye become perceived much closer together. Correction of ptosis accompanying third nerve palsy is usually easily accomplished but carries some risk of corneal exposure.

FOURTH NERVE PALSY
Clinical Features

Fourth nerve palsy presents with vertical diplopia and is commonly accompanied by compensatory contralateral head tilt.[47] Identification of a fourth nerve palsy in a patient with vertical diplopia involves application of the Parks-Bielchowsky three-step test. First, hypertropia suggests weakness of the ipsilateral superior oblique, ipsilateral inferior rectus, contralateral inferior oblique, or contralateral superior rectus muscle. Second, increased hypertropia in contralateral gaze narrows the possibilities to the weakness of the ipsilateral superior oblique or contralateral superior rectus muscles. Third, increased hypertropia on ipsilateral head tilt further reduces the possibilities, ultimately identifying ipsilateral superior oblique weakness.

Although the abnormal ductions may be detected by direct observation, in many cases, patients with vertical misalignment to have no visible impairment in ocular motility (Fig. 10). Therefore, assessment of alignment using alternate cover or Maddox rod testing can be particularly useful to show the characteristic pattern of impaired motility.

The reason that hypertropia is exacerbated in contralateral gaze is that superior oblique palsy causes weakness of depression in adduction (in long-standing cases, the hypertropia in adduction is further enhanced by overaction of the ipsilateral inferior oblique). The reason hypertropia is worse with ipsilateral head tilt is that the ocular counterroll reflex stimulates ipsilateral intorters (superior oblique and superior rectus) and contralateral extorters (inferior oblique and inferior rectus); when the superior oblique is weak, this reflex causes a compensatory increase in ipsilateral superior rectus action, resulting in additional hypertropia (because the superior rectus is an elevator).

Torsional diplopia, which results from ocular cyclotorsion, often accompanies vertical diplopia in acquired fourth nerve palsy. This condition can be quickly assessed by having the patient view a horizontal straight line, such as the edge of a door. A patient with cyclotorsion from unilateral fourth nerve palsy will see a horizontal line
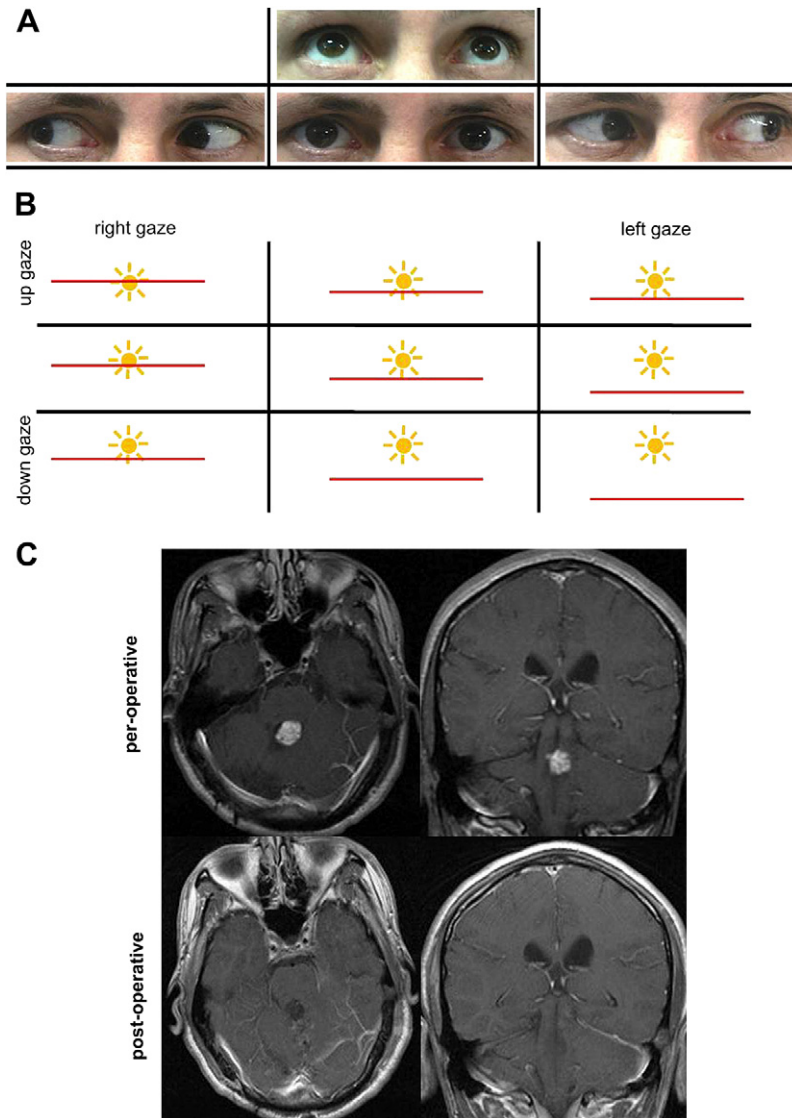
Fig. 10. A 36-year-old man with right fourth nerve palsy following resection of cerebellar hemangioblastoma. (*A*) Essentially normal ductions, with small right hypertropia in primary gaze and upgaze, increased in left gaze. (*B*) Simulation of patient's view through Maddox rod in each direction of gaze. Note greatest vertical separation in down-and-left gaze. (*C*) Pre- and postoperative gadolinium-enhanced T1-weighted MRI scans, showing fourth ventricle hemangioblastoma. (*Reprinted from* Prasad S, Volpe NJ, Tamhankar MA. Clinical reasoning: a 36-year-old man with vertical diplopia. Neurology 2009;72:e93–9; with permission.)

and a second tilted line above or below it, intersecting on the side of the affected eye. Cyclotorsion can also be evaluated with the double Maddox rod, which refracts a light source into one red line (seen by the right eye) and one white line (seen by the left eye). The degree of relative cyclotorsion is measured by rotating the filters until the subject reports that the lines are parallel. Cyclotorsion can also be evaluated during dilated

fundus examination, by assessing the position of the macula with respect to the optic disc. Excyclotorsion of the hypertropic eye suggests fourth nerve palsy because of weakened intorsion; in contrast, intorsion of the hypertropic eye occurs in skew deviation, due to decreased stimulation of the inferior oblique subnucleus.

Assessing cyclotorsion and vertical misalignment in the upright and supine positions may be helpful in distinguishing a fourth nerve palsy from a skew deviation.[48] The misalignment remains fairly constant between these positions in fourth nerve palsy, whereas it is mitigated in the supine position in skew deviation, possibly because the utricular imbalance that causes a skew deviation becomes reduced.[48]

A final clue about the cause of vertical misalignment comes from the fusional amplitude (the ability to fuse disparate images), which suggests the chronicity of strabismus. The fusional amplitude is measured by asking the patient to report double vision while progressively increased prisms are placed over 1 eye. A vertical fusional capacity greater than 8 to 10 diopters suggests the presence of higher compensatory mechanisms that occur with long-standing misalignment, such as a congenital lesion.

Bilateral fourth nerve palsy, which most commonly results from trauma, is characterized by a unique constellation of findings.[49] Primary position vertical alignment may be fairly good because of the canceling effect from bilateral palsies. Esotropia may be present, making the initial diagnosis difficult by potentially suggesting sixth nerve palsies. However, with careful examination, bilateral fourth nerve palsies are readily identified. First, hyperdeviation alternates such that it is contralateral to the direction of gaze and ipsilateral to the side of head tilt. Second, there is esotropia greatest in downgaze (so-called V-pattern esotropia, with >15 prism diopters difference between upgaze and downgaze) because of weakened abduction in depression (the superior oblique acts as an abductor). Third, there is often a large angle of excyclotorsion (>10°), accompanied by prominent torsional diplopia. Rarely, bilateral congenital fourth nerve palsy may occur (**Fig. 11**).

Identifying fourth nerve palsy in the setting of concomitant third nerve palsy can be difficult, because the failure of adduction prevents complete testing of superior oblique function. In this setting, the superior oblique can be evaluated by assessing its
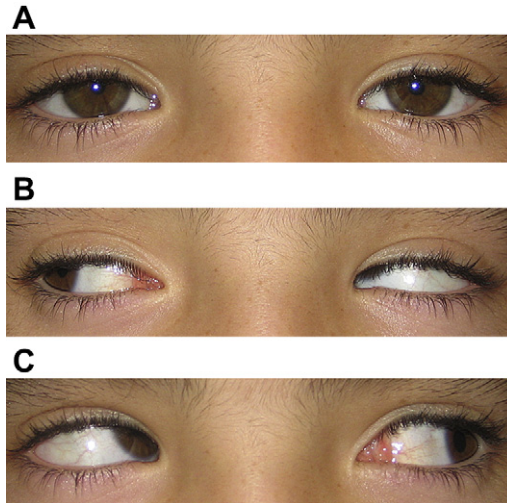

Fig. 11. A 7-year-old girl with bilateral congenital fourth nerve palsy. Brain MRI was normal. (*A*) Normal alignment in primary gaze. (*B*) Left hypertropia in right gaze, with left inferior oblique overaction. (*C*) Right hypertropia in left gaze, with right inferior oblique overaction.

secondary function: intorsion of the abducted eye on attempted downgaze. The torsional movement that indicates intact superior oblique function is best appreciated by observing a conjunctival vessel (**Fig. 12**).

Differential Diagnosis

The most common cause of acquired fourth nerve palsy is trauma.[31,49,50] The trochlear nerve is the longest and thinnest of all the cranial nerves, coursing along the free edge of the tentorium through the prepontine cistern, where it is vulnerable to crush or shearing injury. Fracture of the base of the skull is an alternative cause. In cases of bilateral traumatic fourth nerve palsies, both nerves are often injured at the anterior medullary vellum, where they decussate.[49] Traumatic fourth nerve palsies may occur after minor head injuries without loss of consciousness or skull fractures.

Decompensated congenital fourth nerve palsy is also common and may present in adulthood. There is often a long-standing head tilt, which may be observed on inspection of prior photographs, and an insidious onset of intermittent vertical diplopia. Characteristic features of congenital fourth nerve palsy include inferior oblique overaction, large vertical fusional amplitude, and minimal torsional diplopia. The precise cause of congenital fourth nerve palsy is unclear but may include hypoplasia of the nucleus, birth trauma, anomalous muscle insertion, muscle fibrosis, structural abnormalities of the tendon, or inferior oblique muscle abnormalities.[51] Decompensation later in life probably relates to breakdown of vertical fusion leading to symptomatic diplopia, rather than progressive superior oblique dysfunction.[52]

Microvascular ischemia may cause fourth nerve palsy, typically in patients more than 50 years of age with vascular risk factors. There is often periorbital aching pain on presentation, which can be severe. There is an excellent chance of spontaneous recovery within several months.
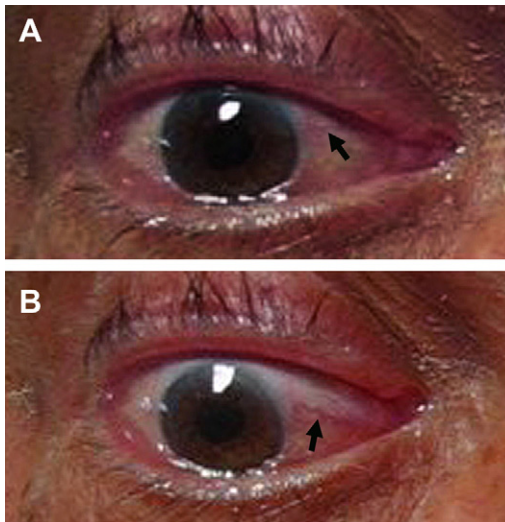

Fig. 12. A 75-year-old man (also shown in **Fig. 20**) with right third nerve palsy from pituitary apoplexy with spared superior oblique function. (*A*) A conjunctival vessel is observed (*arrow*) in primary gaze. (*B*) On attempted downgaze, the conjunctival vessel is observed to move from the 2 o'clock position to the 3 o'clock position (*arrow*), showing intorsion of the eye by an intact superior oblique muscle.

Superior oblique myokymia is a microtremor that causes characteristic episodes of monocular tortional oscillopsia or transient diplopia.[53] It may occur in the primary position or with movements opposite the superior oblique direction of action. It may follow superior oblique palsy or occur spontaneously. Some cases may be due to compression of the fourth nerve by an overlying blood vessel.

Less-frequent causes of fourth nerve palsy include midbrain hemorrhage, infarction, or demyelination.[54,55] Given the proximity to other structures in the midbrain, a lesion of the fourth nerve nucleus or proximal fascicle may cause contralateral superior oblique weakness in association with ipsilateral Horner syndrome,[56] ipsilateral internuclear ophthalmoplegia,[57] or contralateral relative afferent pupillary defect without visual loss (by affecting the brachium of the superior colliculus).[58]

Other causes of fourth nerve palsy include schwannoma, aneurysmal compression, meningitis, hydrocephalus, and herpes zoster ophthalmicus. Inflammatory, infectious, and neoplastic processes that may affect the fourth nerve in the subarachnoid space often cause multiple cranial nerve deficits and are discussed later. When ancillary testing fails to support a definitive cause, a diagnosis of idiopathic acquired fourth nerve palsy can be made.

Management

There are several treatment options for the patient with fourth nerve palsy. Occlusion of the affected eye (or, if diplopia occurs only in down-and-contralateral gaze, occlusion of the lower half of the lens over the affected eye) can serve as a temporary measure when spontaneous recovery is expected. Alternatively, base-down prism over the affected,
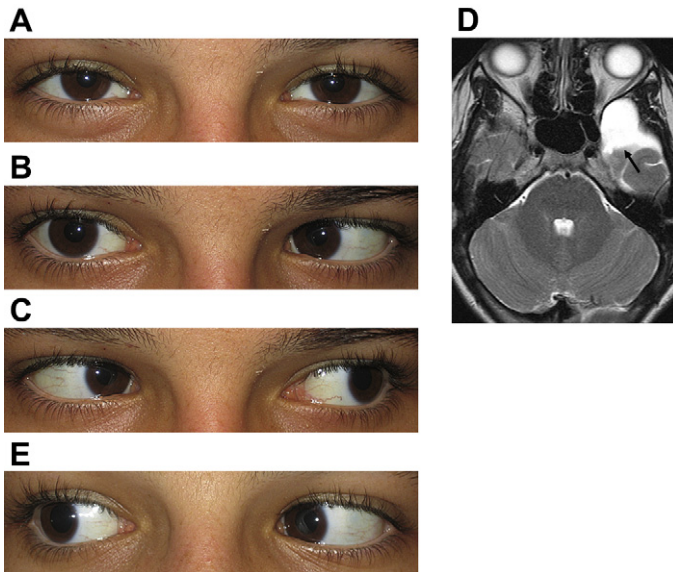

Fig. 13. 15-year-old boy with right sixth nerve palsy due to increased intracranial pressure (54 cm H_2O) in association with an arachnoid cyst. (*A*) Primary position. (*B*) Right gaze, showing right abduction deficit. (*C*) Normal left gaze. (*D*) T2-weighted MRI revealing a left middle temporal fossa arachnoid cyst (*arrow*). (*E*) Two months after surgical decompression of the arachnoid cyst, the right sixth nerve palsy had improved considerably, with a slight residual abduction deficit.

hypertropic eye may be effective. Prisms are generally effective for patients with congenital palsies because they have large fusional amplitudes. However, torsional diplopia cannot be corrected by prisms, and may limit the patient's satisfaction.

Surgery may be necessary for persistent symptomatic fourth nerve palsy when conservative measures fail, as long as the misalignment has been stable for several months. Patients with decompensated congenital fourth nerve palsy generally have a better prognosis after surgery than patients with acquired fourth nerve palsy, because they often have increased vertical fusional amplitude that reduces the likelihood of postoperative diplopia.[59] Selection of the optimal surgical strategy depends
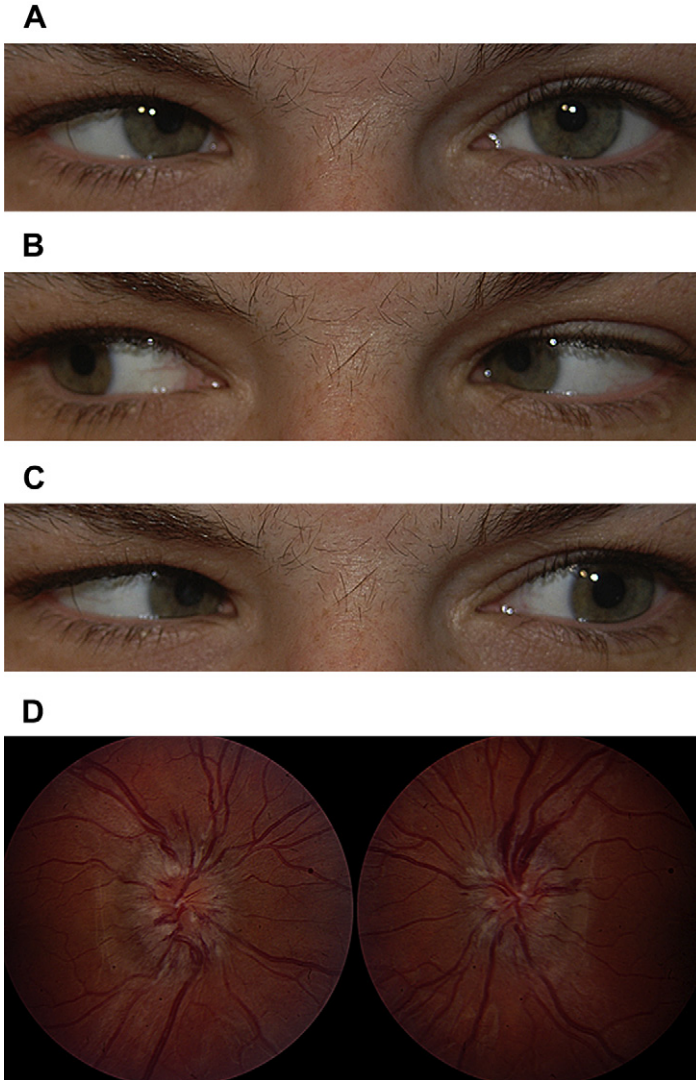

Fig. 14. (*A*) A 29-year-old woman with left sixth nerve palsy due to pseudotumor cerebri following pregnancy. Brain MRI, MR venogram, and CSF constituents were normal. Opening pressure was 35 cm H20. (*A*) Esotropia in primary gaze. (*B*) Normal right gaze. (*C*) Left abduction deficit with intact right adduction.

on the amplitude of deviation and the presence of associated features such as inferior oblique overaction, superior rectus contracture, or superior oblique tendon laxity.[60] In a patient with less than 10 diopters of deviation, recession of 1 muscle may be sufficient. If the inferior oblique shows overaction, it should be selected. However, if the deviation is greater than 15 diopters, then a second muscle should also be recessed. For this purpose, the contralateral inferior rectus or the ipsilateral superior rectus may be selected.[60] Unless superior rectus contracture needs to be addressed, recession of the contralateral inferior rectus may be the superior procedure because it can be performed with adjustable sutures.[46]

The approach outlined earlier can be effective at reducing vertical diplopia. Surgery directly on the superior oblique should generally be avoided in this situation because it carries the risk of iatrogenic Brown syndrome (superior oblique tendon sheath insufficiency). However, with bilateral palsies, or with unilateral palsy causing significant torsional diplopia, the Harado-Ito procedure may be required, in which the anterior portion of the superior oblique is advanced toward the lateral rectus.

SIXTH NERVE PALSY
Clinical Features

Weakness of the lateral rectus due to sixth nerve palsy leads to horizontal diplopia, worse to the affected side and at distance. Often, the abnormal duction is easily observed, but in subtle cases, an incomitant esotropia must be shown by testing binocular alignment.

Differential Diagnosis

Nuclear sixth nerve palsy affects the ipsilateral sixth nerve as well as the interneurons destined for the contralateral medial rectus subnucleus. This lesion causes an
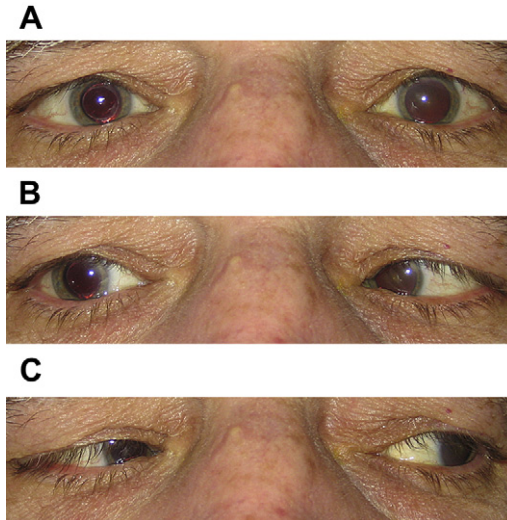

Fig. 15. A 70-year-old man with horizontal binocular diplopia and periorbital aching pain due to microvasculopathic right sixth nerve palsy. Brain MRI and erythrocyte sedimentation rate were normal. (*A*) Slight esotropia in primary gaze. The pupils were pharmacologically dilated. (*B*) Right abduction deficit. (*C*) Normal left gaze. The abduction deficit resolved within 2 months.
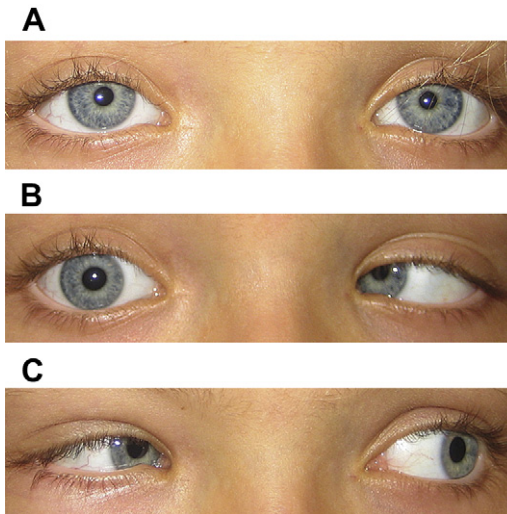
Fig. 16. A 5-year-old girl with right Duane syndrome, type 1. (*A*) Normal alignment in primary position. (*B*) Severe right abduction deficit. (*C*) Full ductions on left gaze, with retraction of the right globe and narrowing of the palpebral fissure.

abduction deficit of the ipisilateral eye as well as an adduction deficit of the contralateral eye; together, this is a conjugate gaze palsy. In contrast, a lesion affecting the sixth nerve fascicle or nerve will produce an ipsilateral abduction deficit but spare adduction of the contralateral eye. Because of the proximity between the seventh nerve fascicle and the sixth nerve nucleus (within the facial colliculus), a single lesion at that location will typically produce ipsilateral gaze palsy and upper and lower facial weakness. A lesion more ventral in the pons may affect the sixth nerve fascicle and the descending corticospinal tract, producing an ipsilateral abduction deficit with contralateral hemiparesis or in isolation. These pontine lesions are commonly ischemic, due to occlusion of a paramedian penetrating branch from the basilar artery, but the differential diagnosis also includes a vascular malformation, demyelination, or neoplasm.[61]

At the base of the skull, as the sixth nerve rises along the clivus over the petrous ligament into Dorello's canal, it is vulnerable to injury from downward mass effect due to
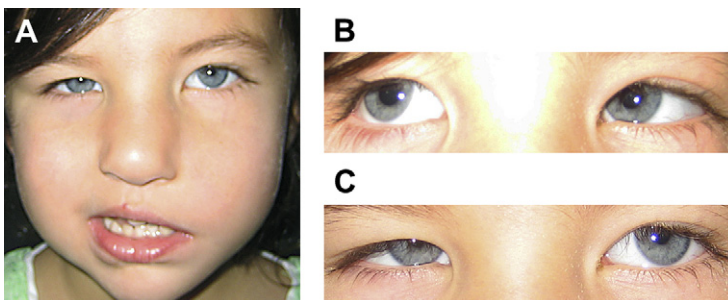

Fig. 17. A 4-year-old girl with bilateral gaze paresis and facial diplegia. (*A*) Upper and lower facial weakness, worse on the left than the right. (*B*) Partial right gaze palsy. (*C*) Marked left gaze palsy.

increased intracranial pressure. Therefore, unilateral or bilateral sixth nerve palsies may occur in the setting of a supratentorial mass (**Fig. 13**), sinus venous thrombosis,[62] hydrocephalus, or pseudotumor cerebri (**Fig. 14**). Conversely, a sixth nerve palsy can also arise in cases of low intracranial pressure, as may occur with a CSF leak.[63] Sixth nerve palsies in these situations tend to improve soon after normal intracranial pressure is restored. Masses growing at the base of the skull, such as meningiomas or chordomas, are also capable of injuring the sixth nerve. These tumors occasionally present with a sixth nerve palsy that has shown spontaneous resolution.[64]

Microvascular ischemia is another common cause of sixth nerve palsies, especially in an elderly patient with vascular risk factors (**Fig. 15**). Similar to other microvasculopathic palsies, these may present with substantial periorbital aching pain. Progression of the abduction deficit in the first week is not uncommon.[65] There is an excellent prognosis for recovery within 3 months.

Severe head trauma is another cause of sixth nerve palsy, which may occur due to shearing forces or fracture of the base of the skull or orbital bones.[31] Gradenigo syndrome refers to sixth nerve palsy in combination with ipsilateral hearing loss and facial pain, which occurs when infectious mastoiditis involves the structures of the
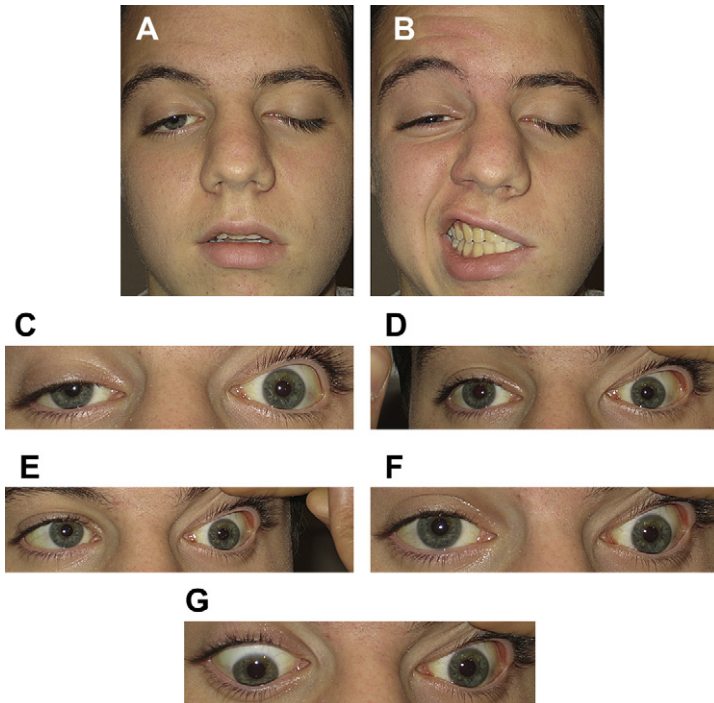

Fig. 18. A 15-year-old boy with multiple idiopathic cranial neuropathies who presented with 3 days of diplopia and facial weakness. There was hyporeflexia and mild ataxia in the arms. Brain MRI was normal and spinal fluid revealed 1 leukocyte and normal protein (55 mg/dL). Anti-GQ1b antibody was negative. (*A*) Bilateral ptosis and facial weakness. (*B*) Upper and lower facial weakness, left greater than right. (*C*) Slight exotropia in primary gaze. (*D*) Severely reduced right abduction and left adduction on attempted right gaze. (*E*) Reduced left abduction and right adduction on attempted left gaze. (*F*) Severely reduced elevation bilaterally on attempted upgaze. (*G*) Reduced depression, left greater than right, on attempted downgaze. Complete resolution occurred within 2 months.

petrous apex.[66] In children, a benign, recurring form of idiopathic sixth nerve palsy may occur, in which esotropia lasts for days to months.[67,68] The diagnostic workup in these cases, including MRI and CSF analysis, is unrevealing.

Congenital abnormalities of the sixth nerve include Duane retraction syndrome and Mobius syndrome. There are 3 varieties of Duane syndrome, which have in common a paradoxic co-contraction of the lateral and medial rectus muscles (**Fig. 16**). This condition causes a visible retraction of the globe and narrowing of the palpebral fissure on attempted adduction. In Duane type 1, abduction is impaired with essentially full adduction; in type 2, adduction is impaired with normal abduction; in type 3, adduction and abduction are reduced.[69] The abduction deficit in types 1 and 3 cause the patient to be esotropic on lateral gaze to the affected side, but these patients can be distinguished from those with acquired abduction deficits because they have normal alignment (rather than esotropia) in primary gaze. Pathologic studies of patients with Duane syndrome show hypoplasia of the sixth nerve nucleus and abnormalities of the fascicle, with branches of the third nerve supplying the lateral rectus muscle.[70,71] Most cases of Duane syndrome are sporadic but, in rare familial cases, defects of the CHN1 gene on chromosome 2 have been identified.[72] Surgical treatment is not necessary for most patients with Duane syndrome, but it can be helpful in rare cases such as those with misalignment in primary position, abnormal head turn, or significant up- or downshoots.[73]
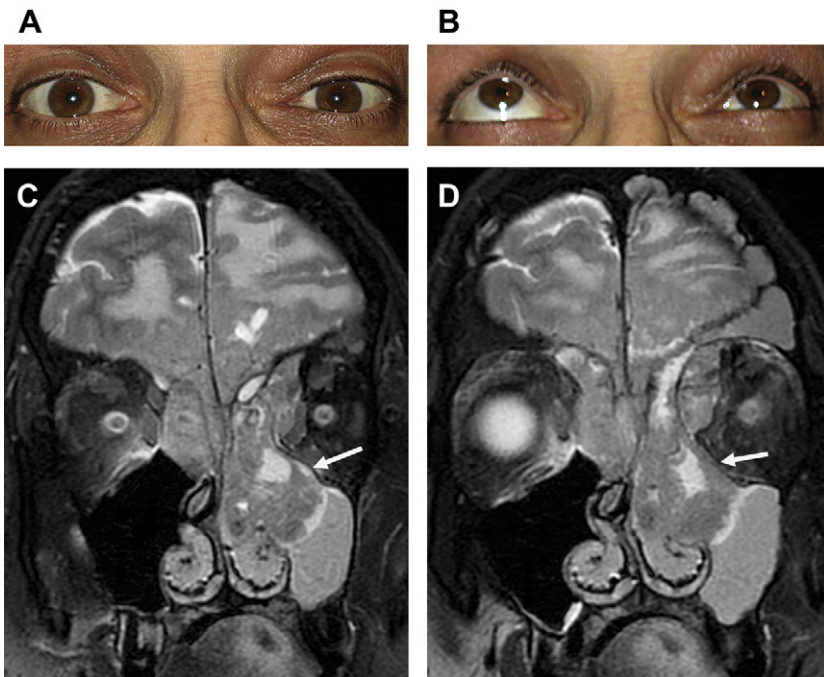

Fig. 19. A 49-year-old man with 1 month of left periorbital swelling and vertical diplopia in upgaze. (*A*) Normal alignment in the primary position, with 5 mm proptosis of the left globe. (*B*) Limited elevation of the left eye in upgaze. (*C, D*) T2-weighted MRI revealing a large mass arising from the left facial sinuses and invading the left orbit supralaterally (*arrow*). Pathologic analysis revealed a highly infiltrating, poorly differentiated epithelial tumor with neuroendocrine features.
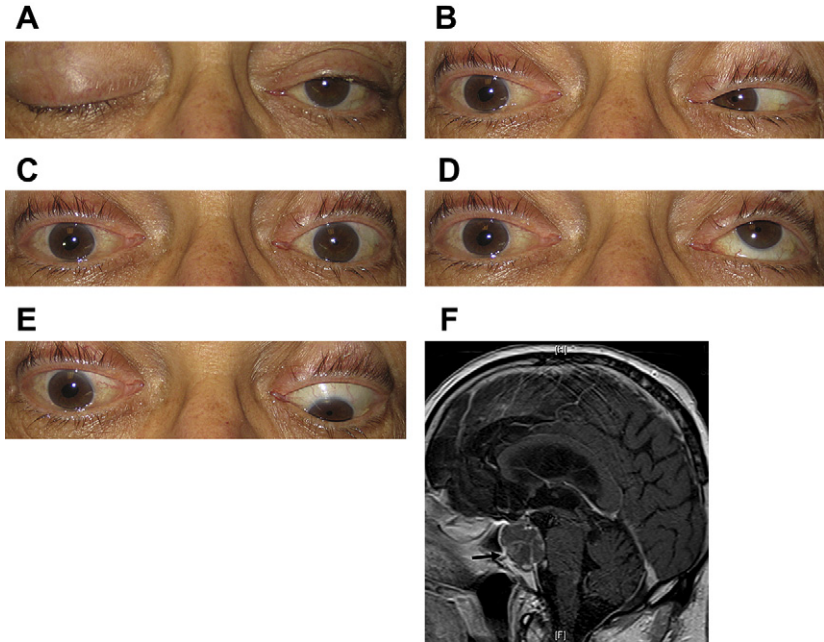
Fig. 20. A 75-year-old man with right third, right sixth, and left sixth palsy due to pituitary apoplexy. (*A*) Complete right ptosis. (*B*) Dilated right pupil and right abduction deficit. (*C*) Complete left abduction deficit and right adduction deficit on attempted left gaze. (*D*) Right elevation deficit. (*E*) Right depression deficit. (*F*) Sagittal postcontrast T1-weighted MRI reveals a heterogeneous mass in the pituitary sella, suggesting pituitary macroadenoma and apoplexy (*arrow*).
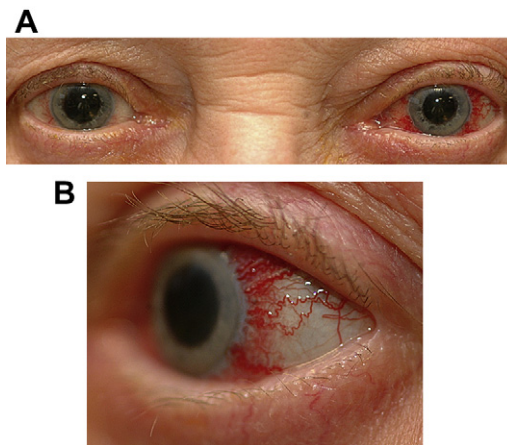

Fig. 21. A 70-year-old woman with headache and left eye redness due to a low-flow (indirect) CCF. (*A*) Left proptosis, periorbital edema, and arteriolization of episcleral vessels. The pupils are pharmacologically dilated. (*B*) Corkscrew arteriolization of episcleral vessels extending to the limbus.

Mobius syndrome describes congenital facial diplegia that is frequently associated with sixth nerve palsy (**Fig. 17**).[74] Conjugate gaze paresis may be present, typically in cases with more severe abduction deficit. Other abnormalities such as complete external ophthalmoplegia, third nerve palsy, or ptosis occur less frequently. The cause of these deficits is believed to be hypoplasia of the relevant brainstem structures.

Other inflammatory, infectious, and neoplastic processes that may affect the sixth nerve in the subarachnoid space are the same as those that can cause third and fourth nerve palsies and other cranial nerve deficits, and are discussed later.

Diagnostic Testing

Many patients with acute sixth nerve palsy require MRI to exclude structural, inflammatory, or neoplastic causes. All children and young adults with sixth nerve palsy should undergo imaging because of a higher prevalence of tumors and demyelinating
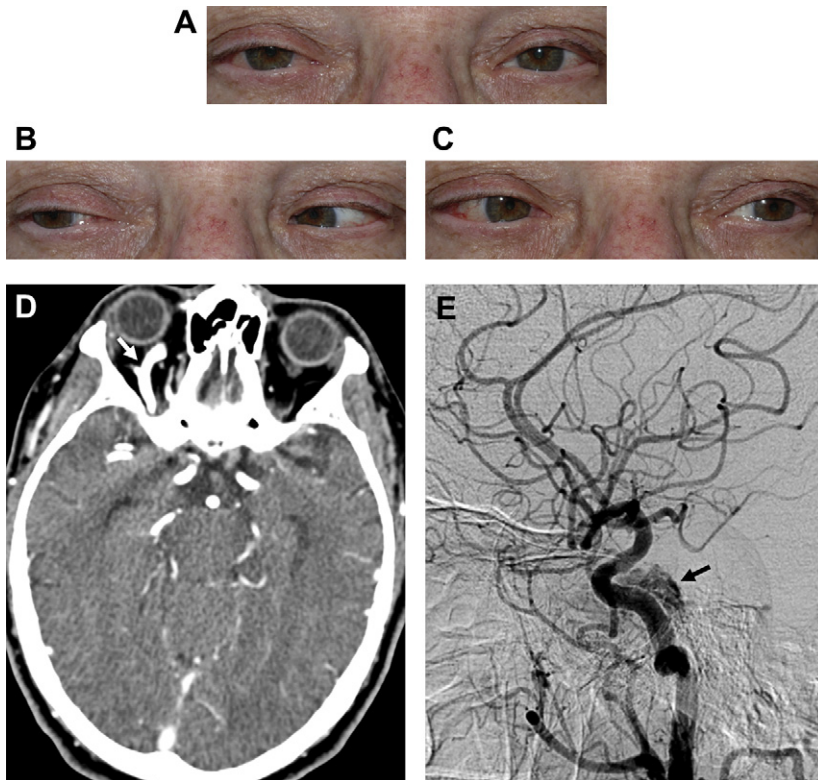

Fig. 22. A 75-year-old man with right CCF who presented with several months of left retro-orbital headache and 2 days of horizontal binocular diplopia. (*A*) Slight esotropia in primary gaze. (*B*) Normal right gaze. (*C*) Limited left abduction. (*D*) CT angiogram revealed dilation and tortuosity of the right superior ophthalmic vein (*arrow*). Catheter angiography revealed a cavernous sinus dural arteriovenous fistula (type D indirect CCF) supplied by bilateral internal and external carotid artery branches (*arrow*) with dominant venous drainage through the right superior ophthalmic vein. The right external carotid supply (via an accessory meningeal artery) was successfully embolized with Onyx 18. Other supplying branches were not amenable to embolization.

lesions.[43,75] However, in a patient in whom a microvasculopathic cause is strongly considered, observation for spontaneous improvement over several weeks may prevent the need for imaging. Additional workup in selected patients with sixth nerve palsy may include serologies and CSF analysis.
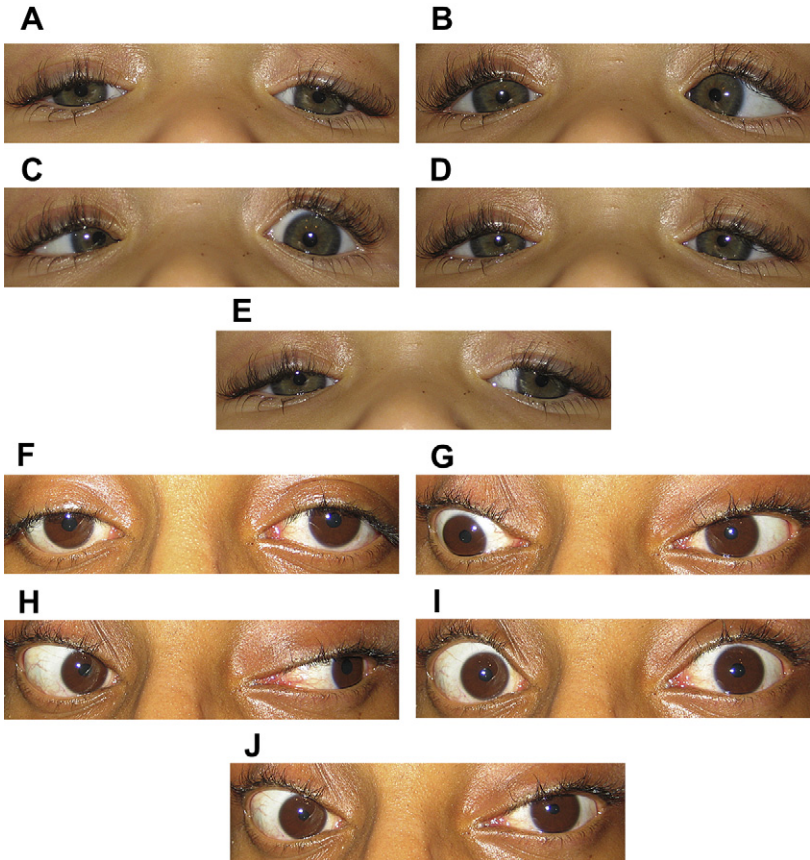

Fig. 23. A 3-year-old boy with ptosis and impaired eye movements, with a family history of similar abnormalities. Sequence analysis of the CFEOM1/KIF21A gene revealed a heterozygous, missense mutation 2821C>T in exon 21, which is a pathogenic mutation associated with congenital fibrosis of the extraocular muscles. He had received prior ptosis surgery. (*A*) Bilateral ptosis, esotropia, and head tilt in primary position. (*B*) Right gaze, revealing right abduction deficit. (*C*) Left gaze, revealing left abduction deficit. (*D*) Severe impairment bilaterally on attempted upgaze. (*E*) Downgaze. (*F*) The patient's father, who had also had surgery for ptosis, in primary gaze with a mild right hypertropia and exotropia. (*G*) Right gaze, showing reduced abduction and adduction. (*H*) Left gaze, showing slight impairments of abduction and adduction. (*I*) Severe bilateral impairments on attempted upgaze. (*J*) Severe bilateral impairments on attempted downgaze. (*K*) The patient's grandfather, with complete right ptosis. (*L*) Right gaze, showing left hypertropia and reduced left adduction. (*M*) Left gaze, showing right hypertropia and mild right adduction deficit. (*N*) Attempted upgaze, revealing severe bilateral impairments with left hypertropia. (*O*) Attempted downgaze, revealing left hypertropia with reduced left infraduction. (*P*) The family tree of the patient (*arrow*) reveals an autosomal dominant inheritance pattern through 5 generations.
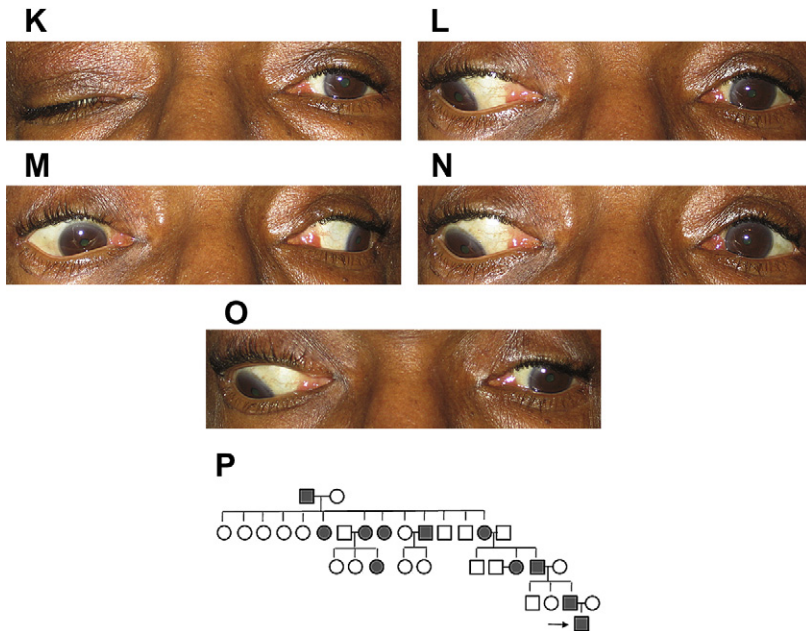
Fig. 23. (*continued*)

Treatment

As with any type of binocular diplopia, the horizontal diplopia resulting from acute sixth nerve palsy may be managed with occlusion or prism. Prism may be helpful to alleviate the compensatory head turn to the affected side. Ultimately, once the amount of eso-deviation has been stable for 6 to 12 months, surgical correction can be considered. Treatment of partial sixth nerve palsy may include a combined medial rectus recession and lateral rectus resection on the affected side. In addition, surgery on the contralateral horizontal rectus muscles may further expand the field of binocular single vision. In cases of complete sixth nerve palsy, the affected lateral rectus is typically left intact to preserve anterior segment circulation. Restoration of abduction on the affected side may be attempted by transposition procedures that aim to move the vertically acting rectus muscles into the horizontal plane. Of these, a full tendon transposition with posterior fixation suture seems to be the most effective, durable procedure.

COMBINED THIRD, FOURTH, AND SIXTH NERVE PALSY

As mentioned earlier, diseases of the subarachnoid space that may affect multiple cranial nerves include infectious, inflammatory, and neoplastic processes. Infectious processes include viral,[76] fungal, or bacterial infection (including tuberculosis, syphilis, and Lyme disease). Inflammatory diseases include sarcoidosis and idiopathic pachy-meningitis. Neoplastic processes include carcinomatous and lymphomatous menin-gitis. Peripheral demyelinating disorders including Guillain-Barre syndrome, the Miller Fisher variant, chronic inflammatory demyelinating polyneuropathy, and idio-pathic cranial neuropathies (**Fig. 18**) are other considerations when multiple ocular motor nerves are involved. Patients with myasthenia gravis may present with complex

patterns of limited eye movements that closely mimic cranial nerve dysfunction, but these patients are often distinguished by the presence of normal pupillary responses.

Expanding masses at the base of the skull can cause compression of multiple ocular motor nerves. One consideration is meningioma of the sphenoid wing (causing ophthalmoplegia, proptosis, and hyperostosis of the temporal bone) or clivus. Other rare possibilities are chordoma, which may arise in the region of the clivus from remnants of the embryologic notochord, or chondrosarcoma, which arises from cartilage in bone.

A process involving the cavernous sinus may affect any combination of the third, fourth, or sixth nerves and cause dysfunction of the first and second divisions of the trigeminal nerve. The differential diagnosis of a superior orbital fissure process and a cavernous sinus process is similar, with the main clinical distinction that the second division of the trigeminal nerve is spared in the former. The differential diagnosis for these syndromes includes neoplastic, infectious, inflammatory, and vascular diseases.[77]

Neoplastic considerations include meningiomas, lymphoma, pituitary adenoma, metastases, trigeminal neuromas, chordomas, chondrosarcomas, and nasopharyngeal carcinomas (**Fig. 19**). Although the slow growth of a pituitary adenoma makes it less likely to involve the ocular motor nerves, the rapid onset of headache and ophthalmoplegia strongly suggests pituitary apoplexy (**Fig. 20**).[78] The third nerve is the most commonly affected by apoplexy, followed by the sixth nerve and lastly the fourth nerve.[79]

Infectious considerations include herpes zoster ophthalmicus, may lead to ophthalmoplegia on the basis of secondary vasculitis or direct inflammation of the ocular motor nerves.[80] Mucormycosis or aspergillosis may spread from the sinuses into the cavernous sinus or orbit, particularly in immunocompromised patients. Tolosa-Hunt is an idiopathic inflammation of the cavernous sinus or superior orbital fissure that causes painful ophthalmoplegia.[81]

Vascular lesions of the cavernous sinus include aneurysms and carotid cavernous fistulas (CCF). Carotid aneurysms may present with pain and diplopia due to involvement of any of the ocular motor nerves, most frequently the sixth nerve. CCFs are characterized as being high flow (direct) or low flow (indirect) based on the source of the feeder vessel and the rate of flow. Most high-flow CCFs result from severe head trauma, but, less frequently, these may arise spontaneously. In some cases, a spontaneous high-flow CCF arises from rupture of a preexisting aneurysm in the cavernous sinus, and in other cases it may occur in the setting of a systemic connective tissue disorder. Patients with a high-flow CCF present with headache, diplopia, proptosis, and severe chemosis. The episcleral veins become dilated and tortuous, extending to the limbus. A bruit may be detected by auscultating over a closed eyelid or, if the CCF drains posteriorly, over the mastoid. Diplopia may occur in these patients because of ocular motor palsy, restrictive myopathy secondary to congestion, or both. An isolated abduction deficit is common, perhaps because the sixth nerve floats freely within the cavernous sinus, near the carotid artery. Other ocular motor palsies may result from direct compression by the expanding fistula or by ischemia due to altered hemodynamics.

In contrast, low-flow CCFs (or dural arteriovenous malformations) are abnormal connections between the cavernous sinus and arteries supplying the dura mater. They are more frequent in elderly women or in association with pregnancy, hypertension, connective tissue disease, or head trauma. The symptoms they produce depend on the route of venous drainage, but are often similar to those produced by a high-flow CCF, including diplopia, proptosis, and chemosis (**Figs. 21** and **22**). However, in a low-flow CCF, these symptoms often have a more insidious onset.

Congenital fibrosis syndromes present with ptosis and a complex pattern of restrictive ophthalmoparesis (**Fig. 23**). Autosomal dominant inheritance is typical and the different clinical forms of congenital fibrosis of the extraocular muscles have recently been linked to specific gene mutations.[82] Surgery can be useful to correct abnormal head position. However, corrective ptosis surgery may lead to corneal exposure, and this risk must be weighed carefully.

SUMMARY

This article discusses the important clinical features that help to distinguish third, fourth, and sixth nerve palsies. These lesions occur in isolation and among other deficits in a host of neurologic disorders. Detailed observations help to ascertain whether a given ocular motor nerve is partially or completely involved, and to determine the topical localization and chronicity of a lesion. These principles guide the formation of an appropriate differential diagnosis, rational clinical decision making, and, ultimately, effective therapies for this group of patients.

ACKNOWLEDGMENTS

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