Diplopia Due to Ocular Motor Cranial Neuropathies

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ABSTRACT

Purpose of Review: Determining which cranial nerve(s) is (are) involved is a critical step in appropriately evaluating a patient with diplopia.

Recent Findings: New studies have looked at the various etiologies of cranial nerve palsies in the modern imaging era. The importance of the C-reactive protein test in evaluating the possibility of giant cell arteritis has recently been emphasized.

Summary: Dysfunction of the oculomotor (third), trochlear (fourth), or abducens (sixth) cranial nerve will produce ocular misalignment and resultant binocular diplopia or binocular blur. A misalignment in the vertical plane of as small as 200 μm is enough to produce diplopia. Diagnosing diplopia from a cranial nerve abnormality requires an understanding of structure (the anatomy of the cranial nerves from nucleus to muscle), function (the movements controlled by the cranial nerves), possible etiologies, and exceptions to the rules.

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ANATOMY

The third cranial nerve (oculomotor) starts in the midbrain as combined midline nuclei divided into subnuclei with a few anatomic quirks that are helpful to know. The superior rectus subnuclei innervate the contralateral eye. The central caudal nucleus is a single nucleus that innervates both levator palpebrae superioris muscles.

These nuclei are located in a dorsal, midline position. Thus, both eyes can be affected with a single nuclear lesion.

The fascicle of the third nerve projects anteriorly, passing by the reticular formation, red nucleus, substantia nigra, and corticospinal tracts to enter the subarachnoid space via the interpeduncular fossa. In the subarachnoid space, the pupillary fibers are located in the superior and medial portion of the nerve. The third nerve passes by the posterior communicating artery, edge of the tentorium, and uncus before entering the upper lateral wall of the cavernous sinus. The third nerve enters the superior portion of the cavernous sinus; it then splits into a superior and inferior division as it enters the orbit through the superior orbital fissure. The superior division supplies the superior rectus and levator palpebrae superioris muscles. The inferior division supplies the medial rectus, inferior rectus, and inferior oblique and, via the ciliary ganglion, innervates the pupillary sphincter and ciliary body.

The fourth cranial nerve (trochlear) nucleus is ventral to the cerebral aqueduct at the pontomesencephalic junction. The axons for each nerve then exit the brainstem dorsally (the only cranial nerve to do so) at the level of the inferior colliculus, where they decussate. The nerve then runs around the cerebral peduncle and enters the lateral wall of the cavernous sinus just below the third nerve, entering the orbit through the superior orbital fissure and innervating the superior oblique muscle. The fourth nerve

has the longest course and fewest axons of the ocular motor nerves. With the decussation, the fourth nerve nucleus innervates the contralateral superior oblique muscle.

The sixth cranial nerve (abducens) nucleus is in the dorsal pons on the floor of the fourth ventricle adjacent to the facial nerve nucleus. The sixth nerve nucleus contains neurons that produce internuclear neurons to innervate the contralateral medial rectus muscle via the medial longitudinal fasciculus. The sixth nerve nucleus along with the fibers from the facial nucleus form the facial colliculus. The axons from the sixth nerve nucleus run ventrally and caudally, lateral to the corticospinal tract, and exit at the pontomedullary junction. The sixth nerve then runs along the clivus until it pierces the dura at the Dorello canal, goes over the petrous ridge, and enters the cavernous sinus. In the cavernous sinus, the sixth nerve is in the middle, just lateral to the carotid artery and medial to the fourth nerve. The sympathetic fibers to the pupil and Mueller muscle are on the sixth nerve for a short distance in the cavernous sinus. The sixth nerve enters the orbit through the superior orbital fissure and innervates the lateral rectus muscle.

FUNCTION

The sixth cranial nerve (lateral rectus) abducts the eye, and the medial rectus (third nerve) adducts the eye. The superior and inferior recti and oblique muscles move the eye in more than one direction, with primary, secondary, and tertiary actions (**Table 9-1**). The superior rectus (third nerve) elevates and intorts the eye with the inferior rectus (third nerve) depressing and extorting the eye. The superior oblique (fourth nerve) depresses and intorts the eye with the inferior oblique (third nerve) elevating and extorting the eye.

Both oblique muscles abduct the eye. The levator palpebrae superioris (third nerve) primarily elevates the eyelid, with the Mueller muscle providing about 2 mm of eyelid elevation.

DIAGNOSIS: LOCALIZATION

In localizing cranial nerve palsies, certain anatomic features can be helpful to limit the possible locations. The first consideration is whether a single cranial nerve (isolated) is involved, and, in the case of the third nerve, whether features that localize to the nucleus or

KEY POINTS

- Diagnosing diplopia from a cranial nerve abnormality requires an understanding of structure (the anatomy of the cranial nerves from nucleus to muscle), function (the movements controlled by the cranial nerves), the possible etiologies, and exceptions to the rules.
- Both the superior and inferior oblique muscles abduct the eye. The levator palpebrae superioris (third nerve) primarily elevates the eyelid, with the Mueller muscle providing about 2 mm of eyelid elevation.

TABLE 9-1 Extraocular Muscle Innervation and Action

Muscle	Innervation	Action[a]
Superior rectus	Oculomotor nerve (superior branch)	**Elevation**, intorsion[b], adduction
Inferior rectus	Oculomotor nerve (inferior branch)	**Depression**, extorsion[c]; adduction
Medial rectus	Oculomotor nerve (inferior branch)	Abduction
Lateral rectus	Abducens nerve	Adduction
Superior oblique	Trochlear nerve	**Intorsion**[b], depression, abduction
Inferior oblique	Oculomotor nerve (inferior branch)	**Extorsion**[c], elevation, abduction

[a] Primary action appears in bold.
[b] Intorsion is the inward rotation of the upper pole of the vertical meridian of the eye.
[c] Extorsion is the outward rotation of the upper pole of the vertical meridian of the eye.

superior and inferior divisions are present. The next consideration is whether multiple cranial nerves are involved, and, finally, whether other neurologic symptoms (eg, hemiparesis, ataxia) are present.

Third Nerve Palsy

Nuclear lesions in the third nerve will produce either bilateral ptosis or no ptosis due to involvement or lack of involvement of the single subnucleus controlling the levator. Similarly, one or both pupils can be either involved or normal because of the rostral location of the paired Edinger-Westphal nuclei. Because of the crossed superior rectus subnuclei, a nuclear lesion will have either bilateral dysfunction, from involvement of the subnuclei and crossing fibers, or contralateral superior rectus dysfunction, from involvement of the crossing fibers only. Fascicular lesions of the third nerve can be associated with hemiparesis, ataxia, or tremor from involvement of adjacent corticospinal tracts, red nucleus, brachium conjunctivum, and cerebellar peduncles. Cavernous sinus lesions can produce third nerve palsies in combination with fourth, fifth (trigeminal) (V1, V2), and/or sixth nerve palsies. In the orbit, either the superior or inferior division of the third nerve can be involved. However, divisional third nerve palsies can occasionally be mimicked by compressive lesions prior to the orbit.

Fourth Nerve Palsy

Isolated nuclear lesions of the fourth nerve are rare and give rise to contralateral palsies caused by the decussation. A nuclear fourth nerve palsy can also include ipsilateral internuclear ophthalmoplegia and Horner syndrome or contralateral afferent pupillary defect from involvement of the medial longitudinal fasciculus, descending oculosympathetic fibers, or pupillary axons in the brachium of the superior colliculus. Cavernous sinus lesions can produce fourth nerve palsies in combination with third, fifth (V1, V2), and/or sixth nerve palsies.

Sixth Nerve Palsy

In the brainstem, a nuclear lesion of the sixth nerve produces a gaze palsy due to the neurons innervating the contralateral medial rectus. A fascicular lesion produces an isolated abduction deficit. Sixth nerve nuclear lesions can damage the adjacent medial longitudinal fasciculus and produce a one-and-a-half syndrome. Fascicular lesions can be accompanied by hemiparesis, sensory change, or facial nerve palsy from involvement of the coriticospinal tract, medial lemniscus, or seventh nerve fascicle. A single clivus lesion, metastasis, or primary tumor can produce unilateral or bilateral sixth nerve palsies, as illustrated in **Case 9-1**. In the petrous ridge, the fifth and sixth cranial nerves can both be affected, typically by infection. Cavernous sinus lesions can produce sixth nerve palsies

Case 9-1

A 51-year-old man presented for evaluation of horizontal, binocular diplopia that had been present for 2 weeks. He was a marathon runner with no vascular risk factors and no family history of vascular disease. On examination he had a right abduction deficit consistent with a right sixth nerve palsy. Neuroimaging was obtained and read as normal. Further review, however, showed that the normal high signal, from fat (**Figure 9-1A**), in the clivus marrow space was absent (**Figure 9-1B**), indicating

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a metastatic process replacing the fat and compressing the sixth nerve in the Dorello canal. Further evaluation revealed other asymptomatic bony lesions, and an eventual diagnosis of metastatic prostate cancer was made.

Comment. In this case, knowledge of the path of the sixth nerve allows a focused review of the MRI and discovery of the abnormality causing the nerve palsy.

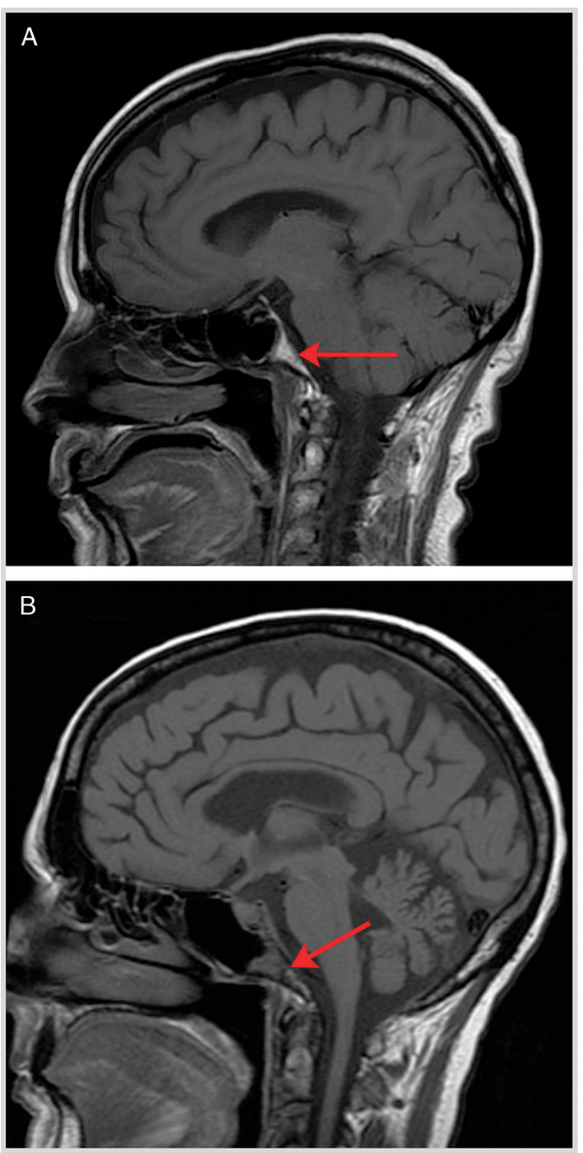

FIGURE 9-1 *Panel A* shows normal high signal in the clivus (*arrow*) on a T1-weighted MRI sagittal MRI of a healthy individual. In *panel B*, the normal high signal, from fat, in the clivus marrow space is absent in the T1-weighted sagittal MRI of the patient in **Case 9-1** (*arrow*), indicating a metastatic process replacing the fat and compressing the sixth nerve in the Dorello canal.

KEY POINT

- Cavernous sinus lesions can produce sixth nerve palsies in combination with third, fourth, and/or fifth (V1, V2) nerve palsies. The combination of a unilateral Horner syndrome and sixth nerve palsy also localizes to the cavernous sinus.

in combination with third, fourth, and/or fifth (V1, V2) nerve palsies. The combination of a unilateral Horner syndrome and sixth nerve palsy also localizes to the cavernous sinus, as illustrated in **Case 9-2**.

Third, Fourth, and Sixth Nerve Palsy

With multiple cranial nerve palsies, four possibilities, or localizations, exist. The first possibility, as already noted, is a cavernous sinus location that involves the third, fourth, and sixth nerves and first and second division of the fifth (trigeminal) nerve (V1, V2), or various combinations. The second possibility for multiple cranial nerve involvement is a CSF-based process affecting the nerves in the subarachnoid space. The third possibility is a neuromuscular junction process, which can mimic a multiple cranial nerve process. The fourth possibility is an inflammatory cranial neuropathy.

Case 9-2

An 86-year-old man reported diplopia that had gradually worsened over the past 3 months. He had no other neurologic complaints. Past medical history included resection of multiple squamous cell carcinomas from his face. Examination showed an abduction deficit on the left, along with left ptosis and miosis (**Figure 9-2**). Testing with cocaine eye drops showed increase in anisocoria with minimal dilation on the left, indicating a left Horner syndrome (**Figure 9-3**). The combination of sixth nerve palsy and Horner syndrome indicated a cavernous sinus localization. The history of slow progression over months indicated a compressive or infiltrative lesion. The history of squamous cell carcinoma indicated perineural spread of the squamous cell carcinoma from the skin through the superior orbital nerve to the cavernous sinus as the etiology. This was confirmed on imaging (**Figure 9-4A**, **B**) and biopsy (**Figure 9-4C**).

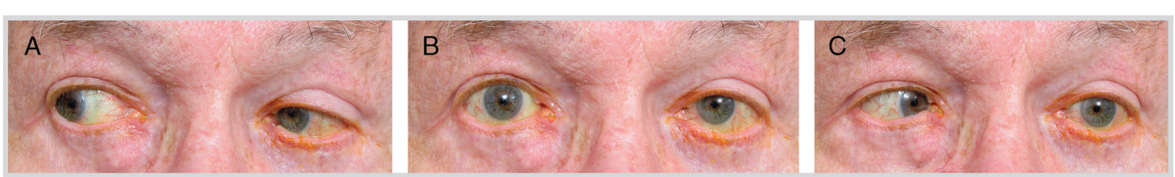

FIGURE 9-2 Examination of the patient in **Case 9-2**. Normal right gaze (*A*), left ptosis and miosis (*B*), and abduction deficit on left gaze (*C*).

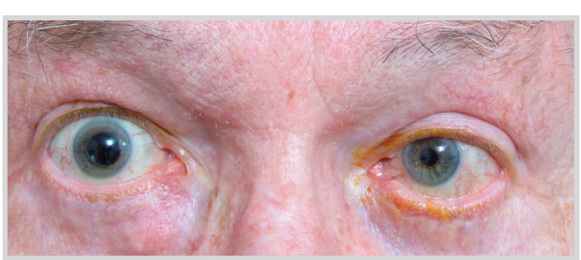

FIGURE 9-3 Testing with cocaine eye drops showed increase in anisocoria with minimal dilation on the left, indicating a left Horner syndrome.

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Comment. In this case the observation of two distinct neurologic findings, a sixth nerve palsy and a Horner syndrome, lead to a single anatomic location, the sixth nerve in the cavernous sinus, and to a focused evaluation and eventual diagnosis.

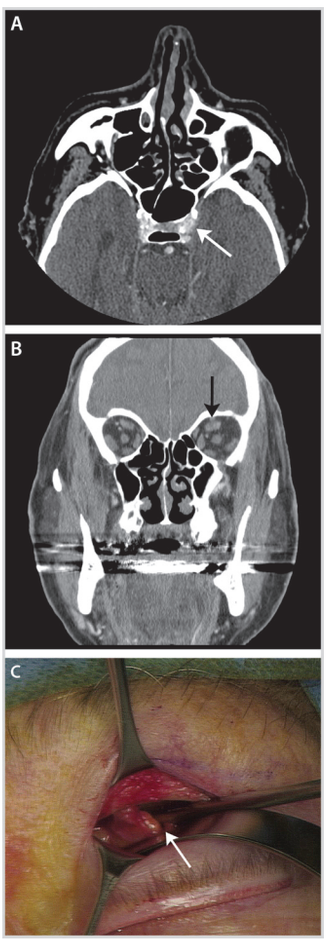

FIGURE 9-4 Imaging and biopsy of the patient in **Case 9-2**. *A*, Fullness of left cavernous sinus on axial CT (*arrow*). *B*, Enlarged superior orbital nerve on coronal CT (*arrow*). *C*, Lid crease incision and biopsy of enlarged superior orbital nerve seen on CT (*arrow*).

DIAGNOSIS: ETIOLOGY

In general, the same processes affect each of the cranial nerves: ischemia, compression, trauma, inflammation, and neuromuscular junction disorders; but differences exist in how common certain etiologies are for each nerve and when multiple nerves are involved. In addition, some conditions are unique to certain nerves, ie, decompensated congenital fourth nerve palsy or aneurysmal third nerve palsy. This section includes

KEY POINTS

- The onset of the diplopia offers no distinction between acute (ischemic) or slow (compressive) etiologies. Occasionally, patients with a compressive lesion will note an increased area in which they see double, ie, double on left gaze becoming double in left, primary, and right gaze over several months.
- Incomplete motor involvement and a normal pupil can be seen with an aneurysmal or other compressive third nerve palsy early on. With progression, motor involvement can become complete and the pupil becomes involved.

discussion on the features common to cranial nerves III, IV, and VI and the features specific to each nerve.

When evaluating any cranial nerve palsy, several questions need to be answered:

1. Are any other neurologic signs or symptoms present? As noted earlier in this article, involvement of the nucleus or fascicular portion of the nerve typically is associated with other neurologic symptoms.
2. Is a history of trauma present? Third, fourth, and sixth cranial nerve palsies can result from trauma, with only minor head trauma needed to produce a fourth nerve palsy.[1]
3. What is the age of the patient? Ischemic cranial nerve palsies occur in patients older than 50 years or in younger patients with significant vascular risk factors.
4. Are any symptoms of giant cell arteritis (eg, new-onset headache, jaw claudication, polymyalgia rheumatica symptoms, fatigue, night sweats, weight loss, fever) present? In this author's experience, 15% of patients with biopsy-proven giant cell arteritis presented with diplopia.
5. Has significant variability in the diplopia occurred, particularly times with and without diplopia in the course of a day? Myasthenia gravis will vary, frequently with no diplopia upon awakening or after a period of rest. Thyroid eye disease will typically produce diplopia that is worse upon awakening and can resolve later in the day because of orbital congestion when supine.

Pain can be severe in ischemic cranial neuropathies and in aneurysmal third nerve palsy or can be absent in either. Given this variability, the presence or absence of pain is much less useful than the other features discussed and therefore is not mentioned in the listing of historical features. In most patients, diplopia is a binary symptom, either present or absent. Thus, the onset of the diplopia offers no distinction between acute (ischemic) or slow (compressive) etiologies. Occasionally, patients with a compressive lesion will note an increased area in which they see double, ie, double on left gaze becoming double in left, primary, and right gaze over several months.

Third Nerve Palsy

In evaluating an isolated third nerve palsy, four additional factors need to be considered when deciding on the etiology:

1. Is the pupil involved, ie, larger than the other pupil and less reactive? Pupillary involvement is considered to be the hallmark of compressive third nerve palsies (rule of the pupil) and relates to the location of the fibers serving the pupil on the outside of the nerve.[2]
2. The extent of involvement of the motor function needs to be evaluated. Are elevation, depression, adduction, and complete ptosis absent? Or are these functions partially affected? This observation is critical because the rule of the pupil only applies in the presence of complete motor involvement. Incomplete motor involvement and a normal pupil can be seen with an aneurysmal or other compressive third nerve palsy early on, as illustrated in **Case 9-3**. With progression, motor involvement can become complete and the pupil becomes involved.[3] There is, of course, an exception to the rule of the pupil. In up to 25% of ischemic third nerve palsies with complete motor involvement, up to 2 mm of anisocoria can be present with the pupil still reactive.[4]

Case 9-3

A 63-year-old woman had 2 weeks of diplopia without headache or other neurologic complaints. She also had hypertension, diabetes mellitus, and a 60 pack-year smoking history. Examination showed mild right ptosis along with mild elevation, depression, and adduction deficits with equally round and reactive pupils, consistent with a partial third nerve palsy with pupil sparing (**Figure 9-5**). While she did have significant vascular risk factors and a normal pupil, because her third nerve palsy was incomplete meant the rule of the pupil did not apply, and evaluation for an aneurysmal third nerve palsy was undertaken. Subsequent CT angiography showed a posterior communicating artery aneurysm **(Figure 9-6).**

Comment. Aneurysmal third nerve palsy is a neuro-ophthalmic emergency where the decision making is driven by careful evaluation of the pupil and extraocular motility. Pain, age, and vascular risk factors do not play a role here.

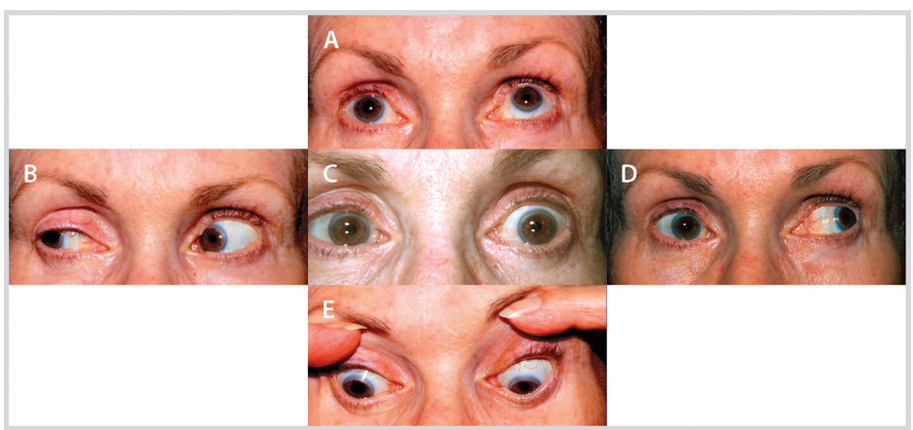

FIGURE 9-5 Examination of the patient in **Case 9-3**. *A*, Upgaze with slight limitation of elevation in the right eye. *B*, Right gaze. *C*, Primary gaze with right ptosis and pseudoretraction on left. *D*, Left gaze with decreased adduction of right eye. *E*, Downgaze with slight limitation of depression in the right eye.

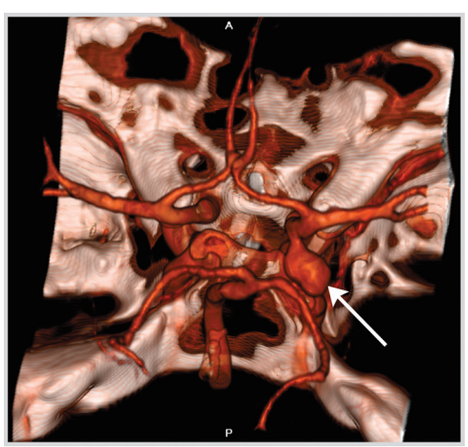

FIGURE 9-6 Reconstruction of CT angiography showing right posterior communicating artery aneurysm (*arrow*).

3. Does the third nerve palsy affect only the superior division or inferior division? This divisional pattern would indicate an orbital process.
4. Are any signs of aberrant regeneration present? Aberrant regeneration consists of an expected gaze movement producing an unexpected or aberrant response. Common examples include eyelid elevation with adduction and ptosis with abduction; adduction with attempted downgaze; or pupillary constriction with elevation, depression, or adduction, as illustrated in **Case 9-4**. Aberrant regeneration is seen either after a traumatic third nerve palsy or with a long-standing third nerve palsy from a compressive etiology, so-called primary aberrant regeneration.[5] Meningioma is the most common cause of primary aberrant regeneration, but aneurysms can also cause this.

Fourth Nerve Palsy

In addition to the usual factors affecting cranial nerves, the fourth cranial nerve can also produce diplopia from decompensation of a long-standing or congenital fourth nerve palsy. This can occur at any age and can be seen with no preceding factors or after trauma or medical illness. A decompensated, congenital fourth nerve palsy has a number of historical and examination features to distinguish it from other recently acquired causes of fourth nerve palsy. When asked, patients with a decompensated, congenital fourth nerve palsy will frequently recall brief episodes of vertical diplopia in the past, usually associated with excessive fatigue or alcohol use. Patients frequently have long-standing head tilt to the side opposite the palsy as a method to reduce symptoms. Review of old photographs can show this head tilt many years prior to the development of symptomatic diplopia. Some patients have facial asymmetry with the side of the face opposite the head tilt being slightly smaller.[6] While these features are variably present, the sine qua non for diagnosing a decompensated, congenital fourth nerve palsy is increased vertical fusional amplitudes or a greater than average ability to fuse two vertically misaligned images into a single image. The normal range for vertical fusional amplitudes is 1 to 4 prism diopters; patients with a decompensated, congenital fourth nerve palsy typically have 6 or more prism diopters of vertical fusional amplitude. This is measured with a prism bar and can be done by neurologists with access to prisms or by neuro-ophthalmologists and ophthalmologists.

Sixth Nerve Palsy

Like the third and fourth nerves, there are special circumstances for an isolated sixth nerve palsy. Alterations in intracranial pressure can produce a sixth nerve palsy, either unilateral or bilateral, from shift of the brain down. With high intracranial pressure, there is associated papilledema. With low intracranial pressure, spontaneous or after lumbar puncture, there will be no other examination findings.

Etiologies by Incidence

When reviewing the frequency of the causes of isolated third, fourth, and sixth nerve palsy, several large series are commonly referenced. A number of these studies, however, raise issues. Some studies have been done prior to modern imaging, some are retrospective or hospital based versus outpatient based, and some from tertiary centers are prone to referral bias. With these caveats in mind, **Table 9-2** and **Table 9-3** give an idea of the prevalence of various etiologies by

Case 9-4

A 45-year-old woman presented with diplopia on upgaze noted recently. She had no history of trauma and no significant past medical, social, or family history. Examination showed mild left ptosis in primary gaze, decreased adduction in right gaze, dilated left pupil in left gaze, adduction of the left eye in upgaze, and left eyelid retraction in downgaze (**Figure 9-7**). This combination of findings indicated primary aberrant regeneration of the left third nerve. Fibers intended for the left medial rectus had regrown to innervate the pupil and physiologically decrease their innervation on left gaze, leading to pupil dilation. Fibers intended for the left inferior rectus had regrown to innervate the levator, leading to eyelid retraction on downgaze. Fibers intended for the left superior rectus had regrown to innervate the medial rectus, leading to adduction on upgaze. The presence of aberrant regeneration without a history of trauma raised a concern for a compressive lesion of the third nerve, typically either cavernous sinus meningioma or long-standing aneurysm. Imaging revealed a cavernous sinus meningioma (**Figure 9-8**).

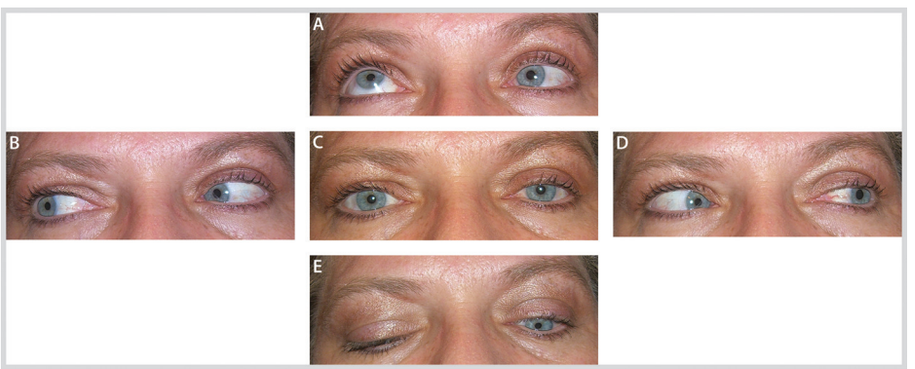

FIGURE 9-7 Examination of the patient in **Case 9-4**. *A*, Upgaze showing lack of elevation of the left eye and adduction of the left eye. *B*, Right gaze showing slight limitation of adduction of the left eye. *C*, Primary gaze showing left ptosis. *D*, Left gaze showing dilation of the left pupil. *E*, Downgaze showing left eyelid retraction.

Comment. The presence of aberrant regeneration indicates either a traumatic third nerve palsy months or years earlier or a long-standing compressive lesion. In the presence of aberrant regeneration, the rule of the pupil or concern for neuromuscular junction disorders no longer applies.

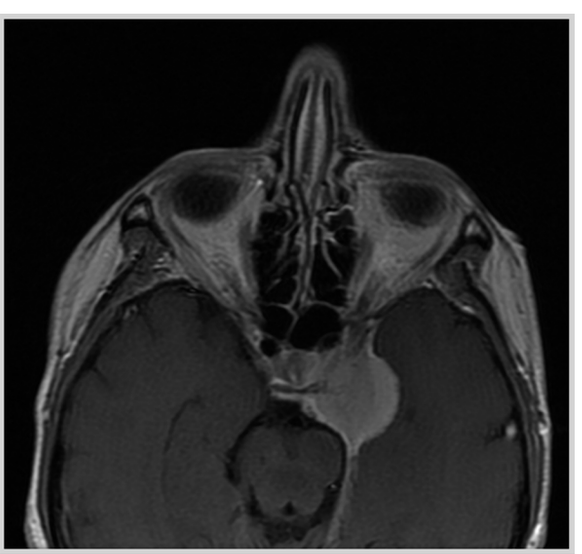

FIGURE 9-8 Axial contrast-enhanced T1-weighted MRI showing a large enhancing cavernous sinus meningioma on the left.

KEY POINT

- Processes adjacent to the cavernous sinus, such as pituitary adenoma, sphenoid wing meningioma, giant aneurysm, and craniopharyngioma, can also affect the cranial nerves in the cavernous sinus.

TABLE 9-2 Etiology of Adult Isolated Cranial Nerve Palsy[a]

Etiology	Cranial Nerve III	Cranial Nerve IV	Cranial Nerve VI
Ischemic	49%	23%	45%
Aneurysmal	9%	0%	0%
Tumor	7%	1%	2%
Congenital	0%	38%	0%
Trauma	6%	29%	15%
Myasthenia gravis	0%	0%	1%
Multiple sclerosis	3%	0%	7.5%
Other	16%	1%	22%
Undetermined	10%	8%	7.5%

[a] Data from Berlit P, J Neurol Sci[7]; Mollan SP, et al, Eye (London),[8] *www.nature.com/eye/journal/v23/n3/full/eye200824a.html*; Patel SV, et al, Ophthalmology,[9] *www.aaojournal.org/article/S0161-6420(03)01184-9/abstract*.

cranial nerve in adults and children.[7–10] Of note is that in the third nerve palsy series myasthenia gravis is included in the "other" category.

Causes of Multiple Cranial Nerve Palsies

When multiple cranial neuropathies are present, two initial questions should be asked:

1. Are the involved nerves in a single anatomic localization, eg, left third, fourth, and sixth nerve palsies from a left cavernous sinus process?
2. Is any sensory involvement present? Myasthenia gravis or Miller-Fisher syndrome can affect multiple cranial nerves but will have no sensory findings.

The cranial nerves in the cavernous sinus can be compromised by either a primary cavernous sinus process, such as meningioma, carotid artery aneurysm, cavernous sinus thrombosis, or idiopathic inflammation (Tolosa-Hunt syndrome), or an adjacent process. Processes adjacent to the cavernous sinus can also affect the cranial nerves in the cavernous sinus. Possibilities include pituitary adenoma, sphenoid wing meningioma, giant aneurysm, and craniopharyngioma.

In the subarachnoid space, multiple nerves, on one or both sides, can be affected by carcinomatous meningitis,

TABLE 9-3 Etiology of Pediatric Isolated Cranial Nerve Palsy[a]

Etiology	Cranial Nerve III	Cranial Nerve IV	Cranial Nerve VI
Tumor	12.5%	1%	17%
Congenital	50%	38%	8%
Trauma	25%	29%	25%
Postviral	0%	0%	17%
Other	0%	1%	0%
Undetermined	12.5%	8%	33%

[a] Data from Holmes JM, et al, Am J Ophthalmol,[10] *www.ajo.com/article/S0002-9394(98)00424-3/abstract*.

TABLE 9-4 Evaluation of Cranial Nerve Palsy

▶ **Cranial nerves (CN) III, IV,[a] VI: Isolated >50 years of age**

CN III: Incomplete or pupil involvement, perform urgent CT angiography/MR angiography; if negative, obtain erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP). Follow-up: Reexamine at 4 weeks and if no better obtain acetylcholine receptor antibodies and directed CN imaging. Consider lumbar puncture and single-fiber EMG.

CN III (pupil sparing, otherwise complete), IV, VI: ESR/CRP done at initial evaluation; if negative then follow up as below.

Acetylcholine receptor antibodies at onset if any variability.

Follow-up: Reexamine at 4 weeks and if no better obtain acetylcholine receptor antibodies and directed CN imaging. Consider lumbar puncture and single-fiber EMG.

▶ **CN III, IV [a], VI: Isolated <50 years of age**

CN III: Incomplete or pupil involvement, perform urgent CT angiography/MR angiography.

CN III (pupil sparing, otherwise complete), IV, VI: Perform directed CN imaging, obtain acetylcholine receptor antibodies/single-fiber EMG and lumbar puncture.

CN III, IV, VI: Single CN palsy with other neurologic features: perform directed imaging depending on other features, anti-GQ1b if any areflexia or ataxia.

CN III, IV, VI (more than one nerve involved): Perform directed imaging to cavernous sinus, skull base, and CN; obtain lumbar puncture, acetylcholine receptor antibodies/single-fiber EMG if no sensory involvement is present.

[a] CN IV with features of congenital decompensation, no evaluation needed.

tuberculosis or other chronic infections, and sarcoidosis.

Myasthenia gravis and Lambert-Eaton myasthenic syndrome can produce weakness simulating multiple unilateral or bilateral cranial nerve palsies. Finally, Miller-Fisher syndrome can produce multiple unilateral or bilateral cranial nerve palsies.

MIMICS AND EXCEPTIONS

Now that the rules have been reviewed, this section will include discussion of the exceptions to the rules.

In patients with previous strabismus surgery, the evaluation of motility to localize to an involved cranial nerve becomes very difficult without knowledge of both the surgery done and the postoperative alignment. Unfortunately, given the common situation of surgery at a young age (eg, age 2) and evaluation with new symptoms at an older age (eg, age 60), the previous data are frequently unavailable.

Strabismus, or congenital ocular misalignment, can produce an esotropia or exotropia potentially misdiagnosed as a cranial neuropathy. Features of the history and examination, however, can distinguish strabismus from cranial neuropathy. A history of patching, eye exercises as a child, or eyeglasses worn only when young suggest a long-standing problem. Typically, patients with strabismus have developed suppression at a young age and will not report diplopia despite obvious ocular misalignment. On examination, strabismus is comitant, ie, the misalignment is equal in all gazes, as

KEY POINT

■ In patients with previous strabismus surgery, the evaluation of motility to localize to an involved cranial nerve becomes very difficult without knowledge of both the surgery done and the postoperative alignment. Unfortunately, given the common situation of surgery at a young age (eg, age 2) and evaluation with new symptoms at an older age (eg, age 60), the previous data are frequently unavailable.

KEY POINTS

- Patients with congenital strabismus can develop acquired cranial nerve palsies. The pattern of misalignment can be difficult to discern until one recognizes the combination of an incomitant and comitant disorder, eg, an incomitant hypertropia from an acquired fourth nerve palsy on top of a congenital, comitant esotropia.
- Duane syndrome can produce an inability to abduct (type 1); inability to adduct (type 2); or inability to abduct and adduct (type 3), mimicking sixth nerve palsy, third nerve palsy, or a combination of both.

compared with the incomitant misalignment seen in acquired cranial neuropathies. Undiagnosed strabismus can be first noticed at a later age.

Of course, patients with congenital strabismus can develop acquired cranial nerve palsies. In this setting, a complaint of diplopia is typical because the new misalignment brings the eyes out of the long-established zone of suppression. The pattern of misalignment can be difficult to discern until one recognizes the combination of an incomitant and comitant disorder, eg, an incomitant hypertropia from an acquired fourth nerve palsy on top of a congenital, comitant esotropia.

Duane syndrome is a mimicker of cranial nerve palsy with several features that can prevent confusion, as illustrated in **Case 9-5**. Duane syndrome can produce an inability to abduct (type 1); inability to adduct (type 2); or inability to abduct and adduct (type 3), mimicking sixth nerve palsy, third nerve palsy, or a combination of both. Four features help distinguish Duane syndrome from cranial nerve palsy: (1) Duane syndrome is congenital, and most patients have suppression and do not report diplopia despite obvious misalignment. (2) In primary gaze most patients are aligned despite marked limitations in abduction or adduction. This contrasts with cranial nerve palsies, in which marked limitations of movement produce misalignment in virtually all gaze positions, including primary gaze. (3) Duane syndrome frequently shows narrowing of the palpebral fissure with adduction, and (4) retraction of the globe (best viewed from the side) occurs with adduction.[11]

Internuclear ophthalmoplegia (INO) can be confused with a partial third nerve palsy, but several features distinguish them:

1. As with patients with Duane syndrome, patients with an INO are aligned in primary despite large adduction deficits. The exception to this rule is patients with bilateral INOs who are exophoric, termed wall-eyed bilateral INO or WEBINO.

Case 9-5

A 27-year-old woman was sent for evaluation of a sixth nerve palsy after a fall from a horse. She reported no loss of consciousness but did see stars. She had no complaints of diplopia. Upon examination, she had absence of abduction on left gaze. She had normal alignment in primary gaze and narrowing of the left palpebral fissure (**Figure 9-9**) on right gaze. All of these findings were consistent with a congenital Duane syndrome. No further evaluation was needed.

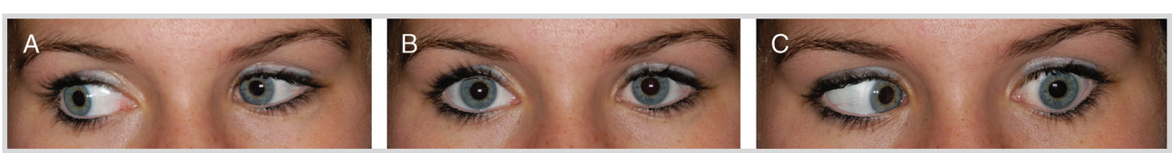

FIGURE 9-9 Examination of the patient in **Case 9-5**. *A*, Right gaze showing narrowed palpebral fissure in the left eye. *B*, Primary gaze showing normal alignment. *C*, Left gaze showing very limited abduction of the left eye.

Comment. This case demonstrates typical findings of an adult with Duane syndrome.

2. Patients with INOs have no other signs of third nerve dysfunction, and a complete adduction deficit without other third nerve findings is extraordinarily rare.
3. Patients with an INO can have an associated skew deviation, with the higher eye being on the side of the INO, that would not be seen with a third nerve palsy.

EVALUATION

The decision on testing rests on three features: (1) Is more than one cranial nerve involved? (2) Is the patient younger or older than 50 years? (3) Which nerve is involved? All cases with multiple cranial nerve palsies or single cranial nerve palsies in patients younger than age 50 need evaluation (**Table 9-4**). Exceptions to the age rule exist, however. Occasionally a patient younger than age 50 will already have previous significant vascular disease. When the third cranial nerve is the involved nerve, special circumstances apply. An incomplete or pupil-involved third nerve palsy requires urgent evaluation for the possibility of an aneurysm regardless of age. The author's institution favors CT angiography (CTA) done the same day a patient is seen as a fast, effective tool to determine whether an aneurysm is present. Others prefer magnetic resonance angiography (MRA) or digital subtraction angiography.[12] The author's argument for CTA is the ease of obtaining the test, the speed of the test, and the fact that motion artifact that can degrade an MRA is rarely an issue. Once obtained, the image must be correctly interpreted. In one series, eight of 17 studies that showed an aneurysm were initially read as normal. When the patient was seen at a tertiary center, the previously conducted studies were reviewed, and an aneurysm was found.[13]

In evaluating an isolated cranial nerve palsy in the patient older than age 50 (excluding partial or pupil-involved third nerve palsies mentioned earlier) erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be drawn. If test results are abnormal or a high level of clinical suspicion is present, the diagnosis of giant cell arteritis should be pursued.[14] Vertical fusional amplitudes should be measured in fourth nerve palsy to diagnose a decompensated congenital fourth nerve palsy that needs no additional evaluation. The diagnosis at this point, assuming normal ESR and CRP, is that of a nonarteritic ischemic cranial nerve palsy, which should recover during the next 1 to 12 months. Some disagreement exists on the need to image these patients immediately to confirm the diagnosis of ischemic cranial nerve palsy (by ruling out a compressive or inflammatory lesion) versus following the patients and obtaining imaging at 4 to 6 weeks if the expected recovery, typically partial at that point in time, has not occurred.[9,15,16] This author favors following patients and imaging at 4 to 6 weeks if no recovery has occurred. In patients in whom a lesion is found at 4 to 6 weeks, typically the delay has no affect on prognosis, and the incidence of a compressive lesion absent a history of cancer is quite low. An acetylcholine receptor antibody titer should be drawn at onset if a history of significant variability is present, or at 4 to 6 weeks if the expected improvement has not occurred. A rest test can also be done to evaluate for myasthenia gravis. The patient is rested for 30 minutes and evaluated for changes, either improvement of the prerest ocular motility abnormality or development of a new abnormality (ie, right hypertropia changing to a left hypertropia with rest), or 2 mm or more improvement in ptosis. If positive, the rest test is highly suggestive for myasthenia gravis.[17] If

KEY POINTS

- In primary gaze most patients with Duane syndrome are aligned despite marked limitations in abduction or adduction. This contrasts with cranial nerve palsies, in which marked limitations of movement produce misalignment in virtually all gaze positions, including primary gaze.
- An incomplete or pupil-involved third nerve palsy requires urgent evaluation for the possibility of an aneurysm regardless of age. CT angiography done the same day the patient is seen is a fast, effective tool to determine whether an aneurysm is present.

imaging is normal and further worsening occurs, lumbar puncture looking for neoplasm, inflammation, or infection can be done.

SUMMARY

The anatomy and physiology of the ocular motor system is well described, and examination of the ocular motor system can be quite precise and quantifiable. This combination of understanding and examination ability allow for accurate diagnosis of ocular motility abnormalities (eg, third nerve palsy). Then, by following the rules described above, as well as understanding the exceptions, diagnostic testing can be appropriately utilized and the cause of the ocular motor abnormality found.

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