Binocular Diplopia
A Practical Approach

Janet C. Rucker, MD, and Robert L. Tomsak, MD, PhD

Background: Diplopia is a common complaint in both inpatient and outpatient neurologic practice. Its causes are many, and special historical and examination features are important to localization and accurate diagnosis.

Review Summary: This review is divided into 2 sections: the first related to diagnosis and the second to treatment of binocular diplopia. In the diagnostic section, emphasis is placed on identification of historical and examination features that can help to differentiate diplopia caused by dysfunction of cranial nerves versus neuromuscular junction, or orbital extraocular muscle. Techniques available to the neurologist for examining ocular motility and ocular misalignment and focused laboratory testing to evaluate diplopia are discussed in detail. The final section covers the various treatments for binocular diplopia, with recommendations regarding the utility of each treatment for different types of diplopia.

Conclusions: A logical step-by-step approach applied to each patient with diplopia will help prevent misdiagnosis and improve patient care.

Key Words: binocular diplopia, Maddox rod, ocular motility, optical prisms

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Diplopia, or double vision, is a frequently encountered and challenging chief complaint in neurology, and the spectrum of disorders that can result in diplopia ranges from emergencies with high morbidity and mortality to benign lifelong conditions. Normally, when an object of interest is viewed binocularly, the image falls on the fovea in each eye and a single image is perceived. When the eyes are misaligned, the object of interest falls on the fovea in 1 eye and on an extrafoveal location in the other eye; thus, 2 images are perceived, resulting in binocular diplopia.

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As in the common approach to most neurologic symptoms, it is essential to have a structural framework based on neuroanatomy with which to analyze the complaint of diplopia. The goal of this review is to present a general approach to the diagnosis and management of common causes of binocular, acquired diplopia. Significant attention is given to historical and examination differentiation of diplopia attributable to common diseases of cranial nerves, the neuromuscular junction, and orbital extraocular muscles. Localization is the foremost task when confronted with diplopia as a chief complaint.

DIAGNOSIS

History

Determination of the binocular nature of the visual complaint is the most important initial historical feature for the neurologist. Diplopia is the most common complaint with ocular misalignment; however, occasionally the patient may complain of visual blurring that resolves with covering either eye as a manifestation of ocular misalignment. It is also helpful to keep in mind that the patient with poor vision in 1 or both eyes may not experience diplopia with ocular misalignment. The patient should be asked specifically if each eye was covered, and it should be confirmed that the diplopia resolves completely with monocular vision. Some patients will not be able to answer this question, but if it is determined that the diplopia is present with monocular viewing, the problem is very unlikely to be neurologic in origin. Rather, refractive error or other ocular causes are likely responsible.[1–3] If monocular diplopia resolves when the patient views through a pinhole, a refractive error can be presumed as the definitive cause.

When binocular diplopia is confirmed, it should be determined if the diplopia is horizontal, vertical, or oblique; if it is worse in a particular direction of gaze; and if it is worse at distance or near. Horizontal diplopia is usually caused by impaired abduction or adduction of an eye, and vertical diplopia results from impaired elevation or depression. Diplopia worse in a particular direction of gaze suggests that ocular motility in that direction is impaired. Diplopia worse at

distance usually accompanies impaired abduction or divergence of the eyes, and diplopia worse at near accompanies impaired adduction or convergence. The astute patient able to answer each of these questions may allow the physician to localize the problem in the first few minutes of the visit. For example, if a patient describes binocular, horizontal diplopia that is worse on right gaze and worse at distance, this is highly suggestive of impaired abduction of the right eye. Care should be taken not to diagnose a specific localization too early, for if a right sixth nerve palsy is diagnosed in the above example, the possibilities of myasthenia gravis or a restrictive medial rectus problem in the right eye may be overlooked.

Determination of the binocular nature of the visual complaint is the most important initial historical feature for the neurologist.

Additional important historical features include the onset, duration, and temporal course of the diplopia. Acute-onset, constant diplopia evokes an entirely different differential diagnosis than intermittent, longstanding episodes of diplopia. If not persistent, the frequency and duration of diplopia episodes should be noted. Diplopia enhanced by fatigue or sunlight may suggest neuromuscular junction disease, whereas diplopia worse in the morning may suggest an extraocular muscle localization. This complaint is particularly prominent with thyroid eye disease, and the mechanism is likely enhanced venous congestion in the extraocular muscles while the patient is in the supine position.

Historical features associated with diplopia are often important in establishing the diagnosis. The patient, and more importantly the family members, should be questioned regarding a persistent head turn or head tilt. This will be discussed further in the examination section. The presence or absence of pain and headaches should be noted and, if pain is present, this usually suggests an inflammatory or ischemic etiology. The patient should be specifically questioned about proximal muscle weakness (eg, does the patient have difficulty holding the arms above the head or ascending stairs?), shortness of breath, and difficulty swallowing. Affirmative answers to these questions may suggest neuromuscular junction disease as the cause of diplopia. Changes in facial appearance, deterioration of monocular vision, eye protrusion, or facial swelling may suggest orbital disease. Facial numbness, ptosis, or a change in pupil size affirmed by history are also helpful in localization. Associated neurologic symptoms, such as vertigo, imbalance, or hemiparesis, should be sought. Past medical history should include questioning regarding ocular or head trauma, history of childhood strabismus or eye muscle surgery, history of facial skin cancer, diabetes, thyroid disease, or immunosuppression.

Examination

A complete and detailed neurologic and neuro-ophthalmologic examination is necessary for accurate localization of binocular diplopia, and familiarity with extraocular muscle function and neurologic innervation is required. Six extraocular muscles control the movements of each eye: medial rectus, lateral rectus, superior rectus, inferior rectus, superior oblique, and inferior oblique. The medial rectus, superior rectus, inferior rectus, and inferior oblique are innervated by cranial nerve III, the oculomotor nerve. The oculomotor nerve also innervates the levator palpebrae superioris and carries parasympathetic fibers to the pupillary sphincter muscle. The superior oblique is innervated by cranial nerve IV, the trochlear nerve. The lateral rectus is innervated by cranial nerve VI, the abducens nerve. Although a gross oversimplification, it is very helpful from a practical standpoint of localizing binocular diplopia to consider the actions of each extraocular muscle individually (Fig. 1). The superior rectus elevates the abducted eye and secondarily intorts the eye. The lateral rectus abducts the eye. The inferior rectus depresses the abducted eye and secondarily extorts the eye. The inferior oblique extorts the eye and secondarily elevates the adducted

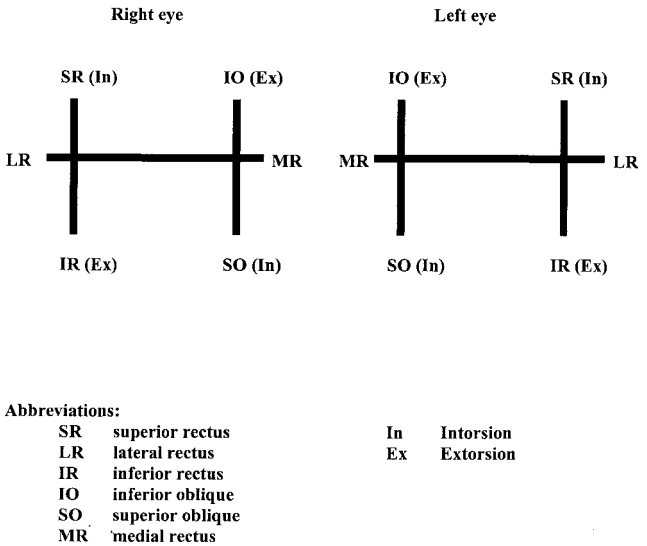

FIGURE 1. Actions of the extraocular muscles. The superior rectus elevates the abducted eye and secondarily intorts the eye. The lateral rectus abducts the eye. The inferior rectus depresses the abducted eye and secondarily extorts the eye. The inferior oblique extorts the eye and secondarily elevates the adducted eye. The superior oblique intorts and secondarily depresses the adducted eye. The medial rectus adducts the eye.

eye. The superior oblique intorts and secondarily depresses the adducted eye. The medial rectus adducts the eye.

Ocular Motility

Examination of ocular motility with careful attention to the range of motion of each muscle is the first step. The eyes are considered to be in primary position when the patient is looking straight ahead. Testing of ductions (1 eye at a time) and versions (both eyes together) in the 9 diagnostic positions of gaze relative to primary position should be performed. The 9 positions include primary position, up, down, right, left, up and right, down and right, up and left, and down and left. Frequently, impairment of eye movements in a specific direction allows the physician to narrow localization. For example, if impairment of abduction of 1 eye is identified, localization can be narrowed to a short list of possibilities: a restrictive process in the ipsilateral medial rectus, disease of the neuromuscular junction, or impaired neurologic innervation of the ipsilateral lateral rectus (cranial nerve VI). It then becomes easier to tailor the rest of the examination and diagnostic testing for further localization.

Ocular Alignment

The second step of the examination includes tests of ocular alignment. At times, a patient experiencing binocular diplopia may appear to have full ocular motility with no impairment of eye movements. This is particularly common with very small ocular deviations and with congenital ocular misalignment. When diplopia is present and ocular motility appears full, tests of ocular alignment are the only examination option for localizing the problem.

Bedside tests of ocular alignment readily available to the neurologist include the corneal light reflection test, cover test, alternate cover test, and the Maddox rod. Understanding of a few central concepts is necessary for correct interpretation of these tests. If it is obvious that there is a manifest deviation of the eyes present, the ocular misalignment is called a **tropia**. If the deviation is not obvious and can only be precipitated by interrupting binocular fusion, the ocular misalignment is called a **phoria**. Esodeviations (esotropia and esophoria) occur with impaired abduction of 1 or both eyes and are defined by 1 eye deviated medially (toward the nose) relative to the other eye. Exodeviations (exotropia and exophoria) occur with impaired adduction of 1 or both eyes and are defined by 1 eye deviated laterally (toward the ear) relative to the other eye. Hyperdeviations (hypertropia and hyperphoria) occur with impaired depression of 1 eye and are defined by 1 eye deviated higher relative to the other eye. Although hypodeviations occur with impaired elevation of 1 eye, by convention, this is generally described as a hyperdeviation in the opposite eye (eg, if the right eye does not fully elevate, this is functionally a right hypotropia; however, it is more commonly described as a left hypertropia).

Comitance

Another key concept in understanding ocular misalignment is the concept of comitance. Comitance refers to the condition in which the amount of ocular deviation is the same regardless of direction of gaze. For example, if a patient has a comitant esotropia, the size of the deviation remains the same in right gaze, left gaze, and primary position of the eyes. In contrast, if an ocular misalignment is incomitant, the size of the deviation changes with changes in the direction of gaze. Generally, cranial nerve and extraocular muscle causes of ocular misalignment produce incomitant deviations. The size of the deviation (and the patient's diplopia) tends to increase in the direction of action of the weak muscle. Perhaps the easiest example to understand is that of a unilateral sixth nerve palsy. If a patient has a right sixth nerve palsy with impaired abduction of the right eye, an esotropia will likely be present in primary position, and it will increase in size with right gaze and decrease in size with left gaze.

Corneal Light Reflection Test (Hirschberg Test)

The corneal light reflection test is a simple, objective test easily performed in a patient with altered cognition or inability to cooperate with more difficult alignment tests. With normally aligned eyes, a light directed toward the patient's eyes from directly in front of the patient will result in a well-centered corneal light reflection with the same position relative to the pupil in each eye (Fig. 2). With ocular

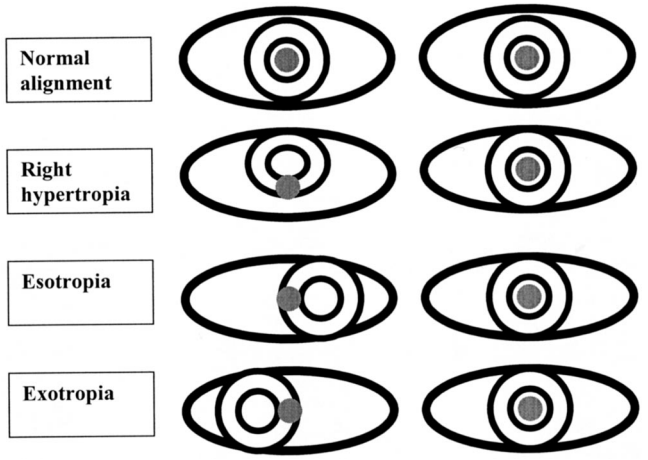

FIGURE 2. Corneal light reflection test. With normal ocular alignment, the light falls in the same position on each cornea relative to the pupil. With a right hypertropia, when the light is placed in the center of the left pupil, the light reflex is below the pupil in the right eye since the right eye is deviated upward relative to the left eye. With an esotropia, when the light is placed in the center of the left pupil, the light reflex is lateral to the pupil in the right eye. With an exotropia, when the light is placed in the center of the left pupil, the light reflex is medial to the pupil in the right eye.

misalignment, when the light is placed in the center of the pupil in 1 eye, it will fall on the cornea in the other eye in a direction opposite to the deviation of the eye. For example, in a patient with an esotropia, when the light is placed in the center of the left pupil, the light in the right eye will fall lateral to the center of the pupil since the eye is deviated medially relative to the other eye (Fig. 2).

Cover and Alternate Cover Tests

For the cover and alternate cover tests, the patient's vision and cognitive status must be adequate to allow maintenance of fixation on an accommodative target (as opposed to a penlight). To perform the cover test, 1 eye is covered and the other eye is closely observed for any movement. If movement is seen, a tropia is present. The test is then repeated on the opposite eye. To perform the alternate cover test, 1 eye is covered and then the other in an alternating fashion, forcing fixation with each eye alternately. The purpose of this is to disrupt binocular fusion in order to detect a phoria. Movements of the unoccluded eye should be carefully noted as the occlusion is alternated. If, for example, the unoccluded eye makes a medial movement to fixate the target each time it is unoccluded, the conclusion may be made that an exophoria is present.

Maddox Rod

The Maddox rod is a subjective test of ocular misalignment that requires an alert, motivated, and cooperative patient. It is best used for small ocular deviations. When properly performed, a large amount of information regarding the type of ocular deviation and the size of the deviation in each direction of gaze can be obtained. With a little practice, the neurologist can easily become proficient at utilizing this effective bedside tool. The Maddox rod, made up of a series of red half-cylinders, is always placed over the patient's right eye (Fig. 3). The examiner shines a light in front of the patient, and the patient should see a red line perpendicular to the alignment of the Maddox rod with the right eye and the white light with the left eye. A horizontal red line (Maddox rod cylinders aligned vertically in front of the patient's right eye) is used to test for vertical ocular misalignment, and a vertical red line (Maddox rod cylinders aligned horizontally in front of the patient's right eye) is used to test for horizontal ocular misalignment (Fig. 3). If normal alignment of the eyes is present, the red line will pass directly through the white light. If an ocular misalignment is present, the red line will be displaced to the right or left of the white light for a horizontal misalignment or superior or inferior to the white light for a vertical misalignment. Once the direction of the misalignment in primary position is established, the size of the misalignment in each pertinent direction of gaze should be assessed to determine comitance or incomitance. A clear red glass placed over the right eye may also be used; however, Maddox rod examination results are easier to interpret.

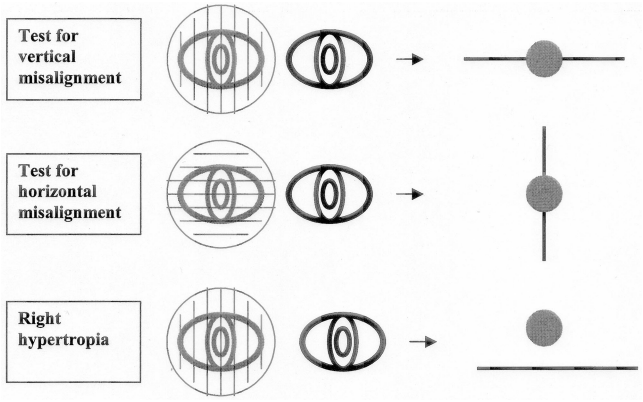

FIGURE 3. Use of the Maddox rod. When the Maddox rod is placed vertically over the right eye, the patient should see a horizontal red line and a white light. When the Maddox rod is placed horizontally over the right eye, the patient should see a vertical red line and a white light. If the eyes are aligned, the red line will go through the white light. If the eyes are not aligned, the red light will be deviated in the opposite direction of the eye relative to the white light. For example, with a right hypertropia, the patient will see the red line deviated below the white light.

Although the neurologist may be able to determine the nature of the ocular misalignment and subjectively quantify its size in different positions of gaze, it is important for the neurologist to consider ophthalmologic or neuro-ophthalmologic consultation for each patient with diplopia. The neurologist rarely has the capacity to objectively quantify the size of an ocular misalignment with optical prisms, and such quantification is required in the event that the patient may be a candidate for ocular realignment surgery in the future.

In addition to careful examination of the ocular misalignment, afferent visual function tests including assessment of visual acuity, visual field, pupillary, and fundus examinations should be performed. All cranial nerves, with special attention to facial sensation, should also be examined. An abnormal head turn or head tilt should be documented, as patients with diplopia may adopt such postures to minimize the diplopia by taking eyes out the direction of action of the weak muscle. Examination findings which strongly suggest cranial nerve, neuromuscular junction, or orbital pathology should be meticulously sought and will be considered in the following sections.

Cranial Nerve Palsies

Third Nerve Palsy (Oculomotor Nerve)

Diagnosis of a complete third nerve palsy is typically straightforward on examination, with an eye that is deviated "down and out," a dilated pupil, and ptosis. Elevation, de-

pression, and adduction of the eye are impaired. Identification of a partial third nerve palsy can be more challenging, especially if the pupil is spared. It should be remembered that neuromuscular junction disease can present with ptosis and impaired elevation, depression, and adduction of the eye. When a third nerve palsy is suspected, evidence of aberrant regeneration (or anomalous axon innervation) should be looked for. To assess for this, watch carefully for elevation of the lid or constriction of the pupil during adduction or depression of the eye (Fig. 4). If aberrant regeneration occurs following an acute third nerve palsy, a compressive posterior communicating artery aneurysm or traumatic etiology is strongly suggested.[4,5] If aberrant regeneration occurs spontaneously without a preexisting third nerve palsy, a cavernous sinus meningioma or internal carotid artery aneurysm is suggested.[6–8]

Fourth Nerve Palsy (Trochlear Nerve)

Cranial nerve IV innervates the superior oblique, which depresses the eye in adduction. With a fourth nerve palsy, the ipsilateral eye is higher than the contralateral eye and the ipsilateral eye may be paretic for downgaze in the adducted position (ie, looking toward the tip of the nose). The vertical deviation will be largest when the patient looks down in an ipsilateral adducted position. The patient usually experiences vertical diplopia, worse on downgaze. There may be a resting head tilt in the direction away from the paretic eye (eg, right fourth nerve palsy, left head tilt). This occurs because the superior oblique not only depresses the adducted eye but also functions as an intorter of the eye. When it is weak from a fourth nerve palsy, diplopia is minimized when the affected eye is in an extorted position. This is accomplished by tilting the head in the opposite direction (eg, right fourth nerve palsy, left head tilt, right eye extorted to minimize diplopia). When a fourth nerve palsy is diagnosed, it is helpful to examine old photographs such as the patient's drivers license to determine if a head tilt can be detected. If so, it is likely that the patient has a congenital fourth nerve palsy and no further workup is needed. However, if there is no evidence of a longstanding head tilt, a new lesion along the course of the fourth nerve should be sought. When vertical diplopia is present but cannot be clearly localized to weakness of the superior oblique, consider the possibility of a skew deviation, which is a common supranuclear cause of vertical diplopia. Neuromuscular junction disease and extraocular muscle weakness may also cause vertical misalignment.

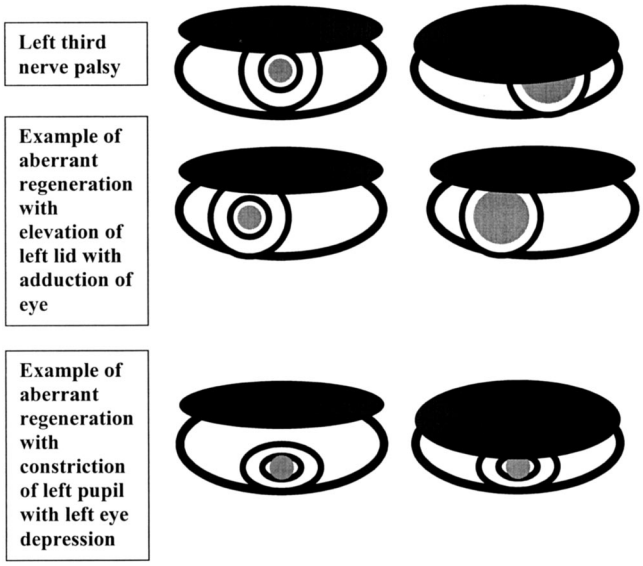

FIGURE 4. Examples of aberrant regeneration following a third nerve palsy. In the first picture, the left eye is ptotic with an enlarged pupil and is deviated "down and out". Upon attempted adduction of the left eye in the second picture, the left lid becomes less ptotic. Upon attempted downgaze of the left eye in the third picture, the left pupil constricts.

Sixth Nerve Palsy (Abducens Nerve)

Cranial nerve VI innervates only the lateral rectus. A sixth nerve palsy results in paresis of abduction of the ipsilateral eye and esotropia. The amount of esotropia is greatest in the direction of action of the weak muscle (eg, right sixth nerve palsy, diplopia and esotropia greatest in right gaze). The patient usually complains of binocular horizontal diplopia.

Determining if the cause of ocular misalignment is restricted to a single cranial nerve may require special examination techniques. Evaluation for a fourth nerve palsy when a third nerve palsy is present requires examination of the affected eye for intact intorsion since depression of the eye is already impaired by the third nerve palsy. To assess intorsion in this setting, the patient should be instructed to abduct the eye and then look down. When dysfunction of more than 1 ocular motor cranial nerve is identified, close examination for facial sensory dysfunction or an optic neuropathy will help determine if the localization may be the cavernous sinus or the orbital apex. Cranial nerves III, IV, VI, and the first and second divisions of V are located in the cavernous sinus. In contrast, the orbital apex contains cranial nerves III, IV, VI, the first division of V, and the optic nerve.

Disorders of the Neuromuscular Junction

Ocular motility dysfunction in myasthenia gravis can mimic nearly any ocular misalignment. Paresis of the muscles in the pattern of a cranial nerve palsy may occur, but the pupil is never involved. A detailed search for features strongly suggestive of myasthenia gravis should be a component of every diplopia examination. These include fatigueability of the eyelids or extraocular muscles with prolonged upgaze,

Cogan's lid twitch, the peek sign, direct orbicularis oculi weakness, ptosis, and enhanced ptosis.[9–12] Variability in the ocular motility examination from visit to visit is also highly suggestive of myasthenia gravis.

Ocular motility dysfunction in myasthenia gravis can mimic nearly any ocular misalignment.

Upgaze should ideally be maintained for at least 2 minutes to adequately assess for appearance or worsening of ptosis or impaired ability to maintain ocular elevation. *Cogan's lid twitch* is assessed for by having the patient sustain downgaze for a few seconds and then make a saccadic return to primary position. In myasthenia gravis, the upper eyelid may elevate too far and twitch and then become ptotic again.[11] The *peek sign* is positive when the patient is able to close the eyes completely initially, but as eye closure is maintained, orbicularis oculi weakness causes the lids to separate to expose the globe.[12] *Enhanced ptosis* is tested for by manual elevation of the most ptotic lid, with observation for increased ptosis in the contralateral lid.[13] The explanation for this phenomenon is equal innervation to the eyelids based on Hering's law. When manual elevation of the most ptotic lid decreases the innervation, the contralateral lid becomes more ptotic. Another phenomenon attributable to Hering's law is that of lid retraction in the eye contralateral to a ptotic lid. Maximal innervation in attempt to keep the ptotic lid open results in excess innervation of the contralateral lid, causing retraction.

Additional information and support of the diagnosis of myasthenia gravis may be obtained if an *edrophonium chloride test* is performed as part of the examination (see Table 1 for details of administering the test).[14] Edrophonium chloride is a reversible acetylcholinesterase inhibitor and, thus, decreases breakdown of acetylcholine in the synaptic cleft, thereby improving neuromuscular transmission. This test is most useful when there is a defined, fixed examination deficit such as significant ptosis or a fixed ocular motility defect that may be unequivocally monitored for improvement after edrophonium chloride administration. Sensitivity and specificity of the edrophonium test in the setting of ocular myasthenia are, respectively, 60% to 80%[15,16] and 86%.[16] There are rare, dangerous, potential risks associated with edrophonium testing, including cardiac arrhythmias, syncope, respiratory failure, and seizures; however, the occurrence of serious side effects is very low, approximately 0.16%.[17] A relatively small dose (mean dose, 3.3 mg) will often result in improvement of the ptosis or ocular motility defect, thereby minimizing potential risks of testing.[18]

TABLE 1. Method for Performing the Edrophonium (Tensilon) Test

1. Identify the examination parameter to be closely observed for improvement following administration of edrophonium; preferably, significant ptosis or a nonflucuating ocular motility defect.
2. Establish an IV line.
3. Prepare all materials before initiation of test.
   10 mg edrophonium in 1 cc syringe
   1 mg atropine
   10 cc saline for IV flush
   Equipment to monitor blood pressure and heart rate
   Video camera, if available
4. Inject 1 mg edrophonium test dose, flush IV, and observe for improvement or side effects such as bradycardia or dizziness over 1 minute.
5. Monitor blood pressure and pulse after this step and subsequent steps.
6. Inject another mg edrophonium, flush IV, and observe for improvement or side effects over 1–2 minutes. Repeat this procedure every 1–2 minutes until positive clinical response achieved, side effects occur, or maximum 10 mg dose is reached.

A second potentially useful test when ptosis is present is the *ice pack test.*[19–21] The premise of this test is that neuromuscular transmission is improved by cold temperatures. This test is administered by placing an ice pack lightly over the closed ptotic eye for 2 minutes, followed by observation for improvement of ptosis. Sensitivity is as high as 80% when partial ptosis is present, but the presence of complete ptosis may decrease sensitivity.[22]

Extraocular Muscle and Orbital Disease

Specific signs of orbital disease include proptosis, chemosis, lid retraction, periorbital edema, and conjunctival injection (Fig. 5). The 2 most common conditions resulting in diplopia secondary to extraocular muscle disease are thyroid eye disease and orbital pseudotumor, or idiopathic inflammation in the orbit. Thyroid eye disease may have unilateral or bilateral onset and is usually painless. Orbital pseudotumor is usually unilateral, with sudden painful onset. Thyroid eye disease classically affects the inferior and medial recti muscles first, leading to restriction of elevation and abduction of the eye. Either disease may result in compression or inflammation of the optic nerve, resulting in a clinical optic neuropathy.

Laboratory Testing

When history and examination clearly suggest localization of the problem, laboratory testing can be tailored. When

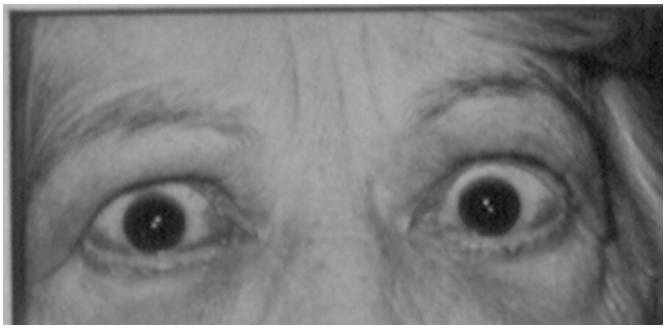

FIGURE 5. Examination evidence of orbital and extraocular muscle disease in a patient with diplopia. Note the lid retraction, conjunctival injection over the extraocular muscle insertions, slight esotropia, and periorbital edema.

there are few or no localizing features in the patient with diplopia, a more general approach is required. Neuroimaging is often the first step in assessment of diplopia, and the technique of choice will vary, depending on the certainty of localization. The most frequently used options are orbital CT scan, MRI of the brain and orbits with gadolinium, and orbital ultrasound. If thyroid eye disease is clearly suspected by history and examination, CT scan of the orbits will usually suffice for identifying enlargement of the extraocular muscles and assessing for compression of the optic nerve (Fig. 6). It is important to examine both axial and coronal images, as muscle enlargement may be underestimated if axial images alone are obtained. When a history of orbital trauma and examination suggest extraocular muscle entrapment from an orbital fracture, CT scan of the orbits is the neuroimaging procedure of choice.

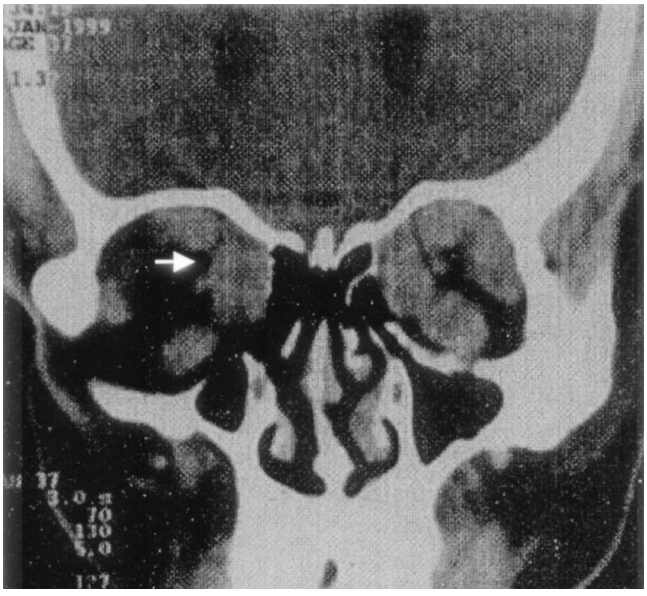

FIGURE 6. Coronal computed tomographic scan of the orbits demonstrating marked enlargement of the medial rectus (arrow) in the right eye and marked enlargement of all extraocular muscles in the left eye.

The 2 most common conditions resulting in diplopia secondary to extraocular muscle disease are thyroid eye disease and orbital pseudotumor.

In most other instances, localization and diagnosis may not be so straightforward and MRI of the brain with gadolinium, high-resolution cuts through the brainstem, and orbital fat suppression images will allow the most complete assessment of the structures which cause diplopia. Diffusion-weighted imaging is also helpful, if brainstem ischemia is in the differential diagnosis. It must be remembered that a standard MRI of the brain with gadolinium will not allow adequate assessment of the orbit, as the bright white orbital fat will obscure orbital pathology (Fig. 7). The most useful current MRI technique for suppression of orbital fat and superior orbital imaging is the long-echo time STIR (short τ inversion recovery).[23]

Cranial Nerve Palsies

The goal of neuroimaging in the setting of an acute-onset, pupil-involving third nerve palsy is evaluation for an intracranial aneurysm. MRI of the brain with magnetic resonance angiography (MRA) is frequently the initial procedure, although the use of CT angiogram is becoming more common. 92% of posterior communicating artery aneurysms causing third nerve palsies are larger than 5 mm.[24] MRI detects aneurysms larger than 5 mm with 97% sensitivity and aneurysms smaller than 5 mm with 54% sensitivity.[24] The rupture risk of an aneurysm less than 10 mm is 0.05% per year.[25] When one takes these statistics into consideration, MRA will miss approximately 1.5% of third nerve palsy-causing aneurysms that will eventually rupture. In the setting of a patient with a negative MRA and a pupil-involving third nerve palsy, it is often prudent to proceed with conventional intracranial angiogram to definitively exclude an aneurysm, given the potential morbidity and mortality involved. After an aneurysm is excluded as the cause of a pupil-involving third nerve palsy, it may be necessary to reimage the patient with an MRI with gadolinium and high-resolution cuts through the brainstem to evaluate for a small inflammatory or neoplastic lesion along the course of the third nerve. If such an MRI is unremarkable, a lumbar puncture may be required to assess

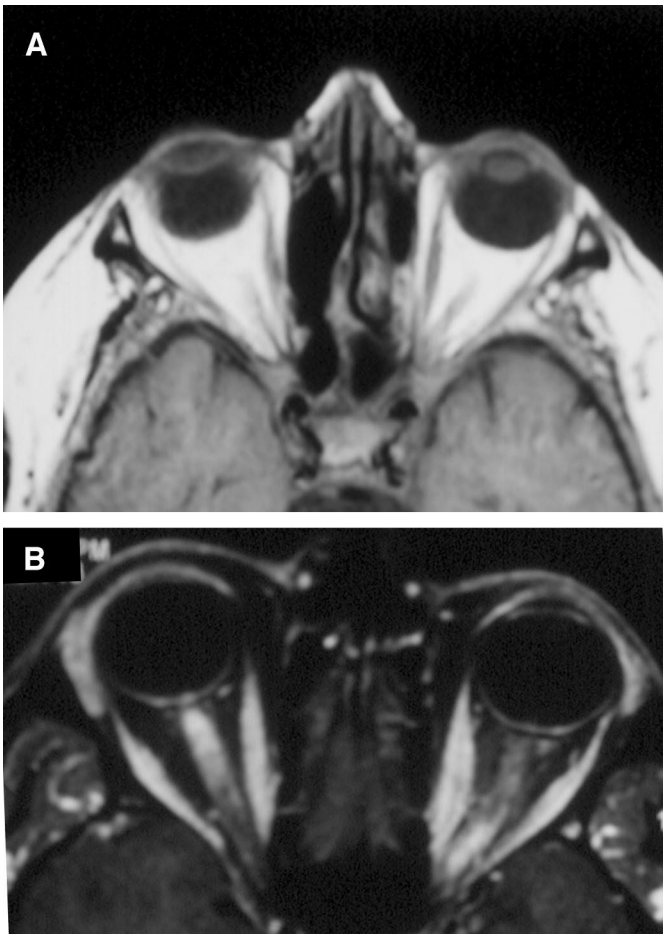

FIGURE 7. A, Orbital appearance without fat suppression on standard brain magnetic resonance imaging. B, Orbital appearance with fat suppression on orbital short τ inversion recovery sequence magnetic resonance imaging.

for inflammation or other cerebrospinal fluid abnormalities. This having been said, the entity of microvascular ischemic third nerve palsies requires discussion.

Magnetic resonance angiography will miss approximately 1.5% of third nerve palsy-causing aneurysms that will eventually rupture.

Acute onset of a painful, pupil-sparing third nerve palsy is often the result of microvascular ischemia to the nerve, especially in middle-aged or elderly patients with vascular risk factors, particularly diabetes and hypertension. It is appropriate in this setting to forgo immediate neuroimaging and to monitor the patient for spontaneous resolution of the third nerve palsy over the next 8 to 12 weeks. If improvement fails to occur, neuroimaging and possibly lumbar puncture become necessary. The MRI in Figure 8 demonstrates why. The patient developed an acute-onset, painful, pupil-sparing third nerve palsy, which failed to spontaneously recover.

Acute onset of a painful, pupil-sparing third nerve palsy is often the result of microvascular ischemia to the nerve.

Neuroimaging in the setting of a sixth nerve palsy is often less emergent than imaging of a third nerve palsy, unless there is evidence by history (headaches with transient visual obscurations or pulsatile tinnitus) or examination (papilledema) of elevated intracranial pressure. As in the case of

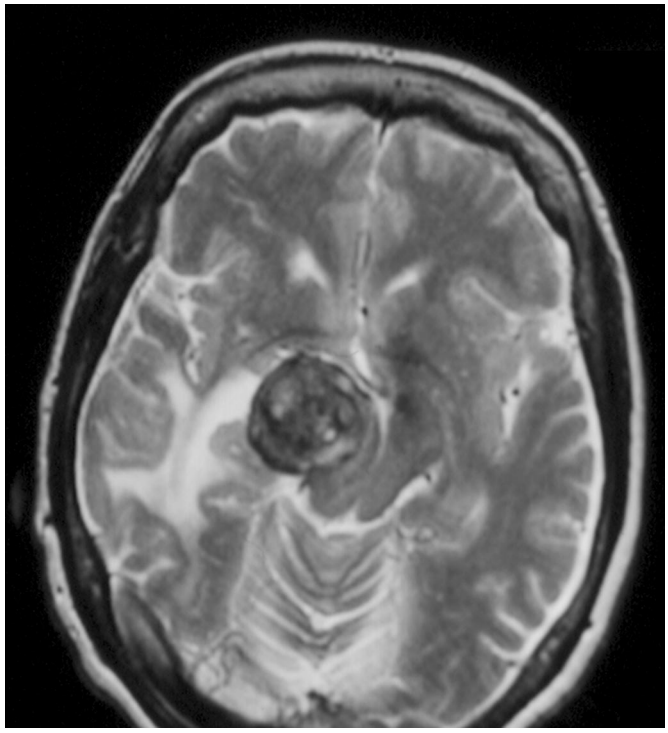

FIGURE 8. Axial T2-weighted magnetic resonance imaging of the brain demonstrating a giant aneurysm responsible for the patient's acute-onset, pupil-sparing, third nerve palsy. The initial working diagnosis was a microvascular third nerve palsy, but it failed to spontaneously improve, and magnetic resonance imaging was obtained.

a suspected microvascular third nerve palsy, if a patient with diabetes or hypertension has the acute onset of a painful sixth nerve palsy, neuroimaging can be withheld and the patient monitored for spontaneous improvement over the next 8 to 12 weeks. If improvement does not occur, MRI of the brain with gadolinium, high-resolution cuts through the brainstem, and fat-suppressed orbital imaging to assess for inflammation, neoplasm, demyelination, etc. along the course of the sixth nerve and to assess for enlargement or enhancement of the medial rectus in the ipsilateral eye should be obtained (Fig. 9). If MRI is unremarkable, lumbar puncture should be performed, with measurement of opening pressure and fluid analysis. It should be remembered that medial rectus involvement in thyroid or other extraocular muscle disease may cause a restrictive process that can mimic a sixth nerve palsy. It is helpful to screen for thyroid dysfunction and myasthenia gravis if a patient has an unexplained abduction deficit.

The diagnostic workup of an acquired fourth nerve palsy is similar to that of the other cranial nerves; MRI of the brain with gadolinium, high-resolution brainstem images, and fat-suppressed orbital images should be followed by lumbar puncture if no etiology is determined. Microvascular fourth nerve palsies are uncommon, so imaging is not typically withheld for this reason. However, congenital fourth nerve palsies are relatively common, and neuroimaging is not necessary if a longstanding nature can be confirmed by history. If there is no evidence of a longstanding head tilt by questioning or review of old photographs, it is prudent to proceed with imaging to assess for a lesion along the course of the fourth nerve (Fig. 10).

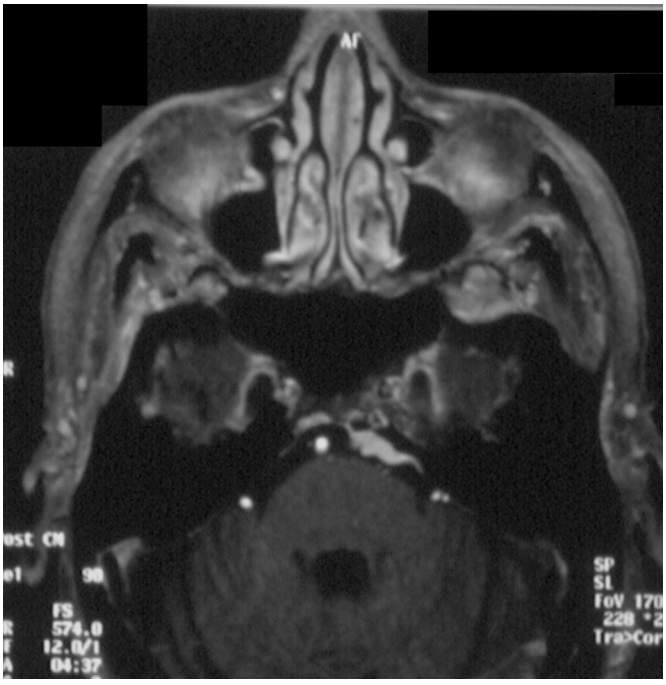

FIGURE 9. Axial T1-weighted magnetic resonance imaging with gadolinium demonstrating a left prepontine en plaque meningioma. The patient is a 70-year-old with diabetes who had an acute-onset, painful, left sixth nerve palsy that failed to improve spontaneously.

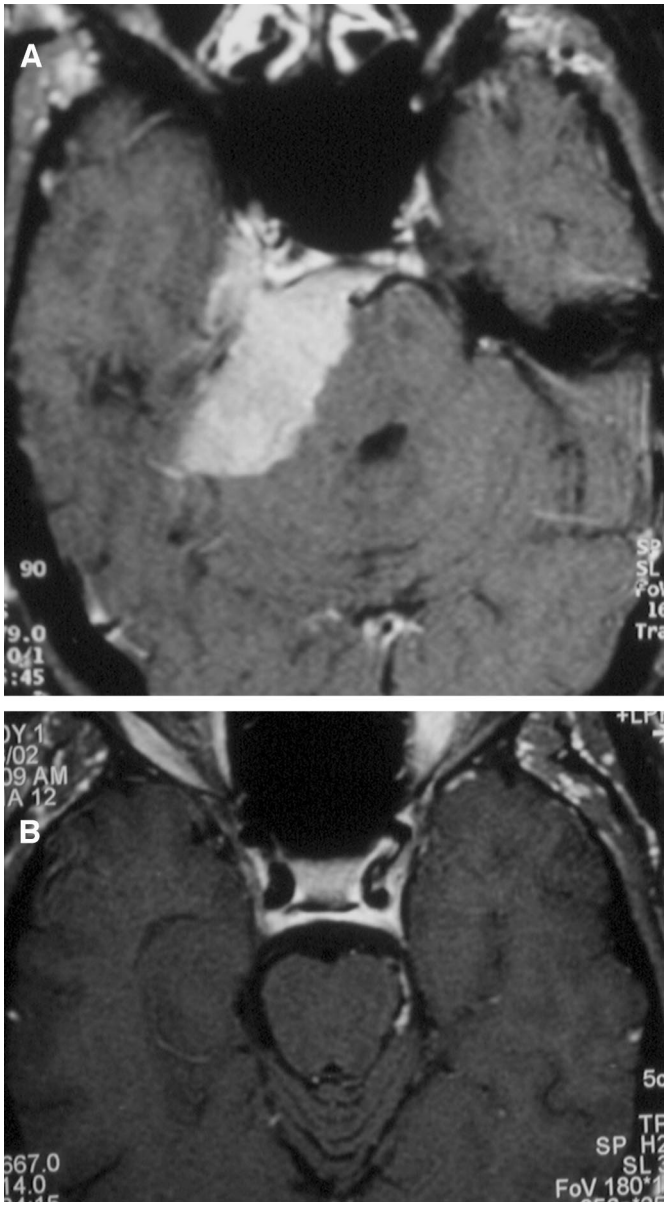

FIGURE 10. A, Axial T1-weighted gadolinium-enhanced brain magnetic resonance imaging in a patient with an isolated, acute-onset, right fourth nerve palsy. A large enhancing mass consistent with a meningioma is seen. B, Axial T1-weighted gadolinium-enhanced brain magnetic resonance imaging in a patient with an isolated, acute-onset, left fourth nerve palsy. A small enhancing lesion of the fourth nerve fascicle consistent with a schwannoma is identified.

When dysfunction of cranial nerves III, IV, and VI occurs in combination, MRI of the brain and orbits with gadolinium will frequently reveal either an infiltrative, inflammatory, or compressive lesion of the cavernous sinus or orbital apex (Fig. 11).

Neuromuscular Junction Tests

Diagnostic testing for myasthenia gravis includes serologic tests and electromyography (EMG). Acetylcholine receptor antibodies consist of 3 types: binding, blocking, and modulating. In generalized myasthenia gravis, binding and modulating antibodies have a sensitivity of 89% and blocking antibodies of 52%;[26] however, these numbers are much lower in pure ocular myasthenia gravis. The sensitivity of acetylcholine receptor antibodies in ocular myasthenia is approximately 50%;[27] thus, the absence of seropositivity does not exclude the disease. More recently, anti-MuSK (antimuscle specific receptor tyrosine kinase) antibodies have been identified in patients with myasthenia gravis previously considered seronegative.[28,29] Anti-MUSK antibodies are not, however, usually identified in patients with purely ocular myasthenia.[30] The prevalence of thyroid dysfunction is higher in patients with myasthenia gravis than in the general population, so it is useful to assess thyroid function studies when myasthenia is suspected, as well.

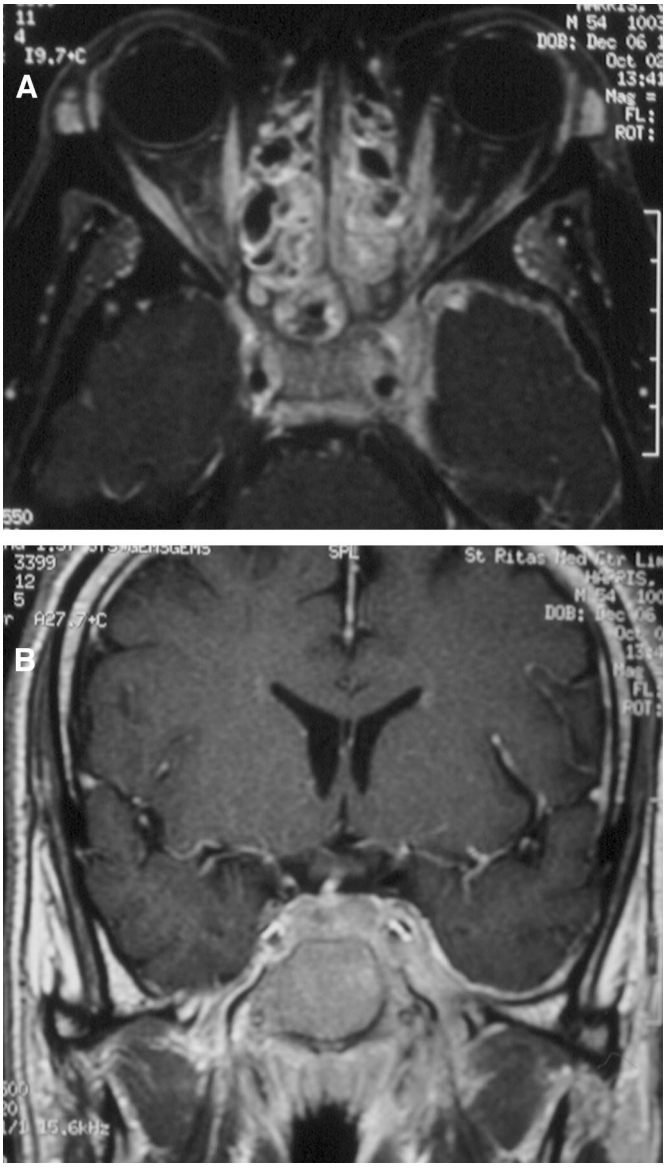

FIGURE 11. Axial (A) and coronal (B) T1-weighted, gadolinium-enhanced brain magnetic resonance imaging in a patient with left third and sixth nerve palsies. Enhancement and enlargement of the left cavernous sinus consistent with an infiltrative infectious, inflammatory, or neoplastic etiology is seen. Also seen is enhancement of the dura surrounding the left temporal lobe tip. Biopsy of the sinuses revealed squamous cell cancer.

EMG with determination of a decrement with repetitive stimulation has a sensitivity of 42% in ocular myasthenia.[31] If it is negative, diagnostic yield can be increased by having the patient, undergo single fiber EMG. This test requires a highly skilled physician for highest yield and is uncomfortable for the patient, but can be performed with up to 100% sensitivity if definitive diagnostic evidence is necessary.[31]

Extraocular Muscle and Orbital Disease Tests

When thyroid disease is suspected, thyroid function studies, including thyroid-stimulating hormone, T3, and T4 should be assessed. Recently, the importance of antithyroid antibodies has been emphasized. Thyroid-stimulating antibodies have been found to be correlated with thyroid eye disease and may even be abnormal in the setting of a euthyroid serologic state.[32] Antithyroglobulin antibodies and antimicrosomal antibodies are occasionally elevated with thyroid eye disease.[32,33]

The importance of fat-suppression orbital imaging has been emphasized in the preceding sections, as has the importance of examining both axial and coronal views to adequately evaluate extraocular muscle size. Enlargement of the extraocular muscles is highly suggestive of thyroid eye disease, especially if the process is painless and the muscle enlargement is in a pattern of medial and inferior rectus muscles with the greatest enlargement (Figs. 6 and 12). If the patient experiences acute-onset, painful diplopia and enlargement of 1 or more extraocular muscles is seen, idiopathic inflammatory orbital pseudotumor or idiopathic extraocular myositis is likely (Fig. 13). It is important to monitor these patients over time, for intraocular lymphoma is also in the differential diagnosis. A radiographic feature helpful in distinguishing enlargement of extraocular muscles from thyroid disease versus orbital inflammation is whether or not the tendon of the muscle is involved. If the tendon is spared (Fig. 12), thyroid disease is more likely. In contrast, if the tendon is also enlarged, orbital pseudotumor is more likely.

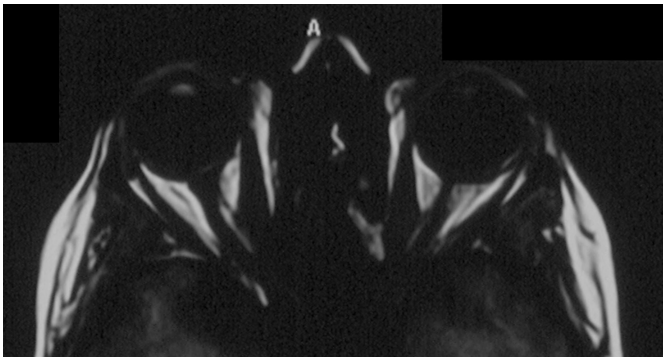

FIGURE 12. Axial T1-weighted brain magnetic resonance imaging demonstrating enlargement of the medial recti bilaterally in a patient with thyroid eye disease.

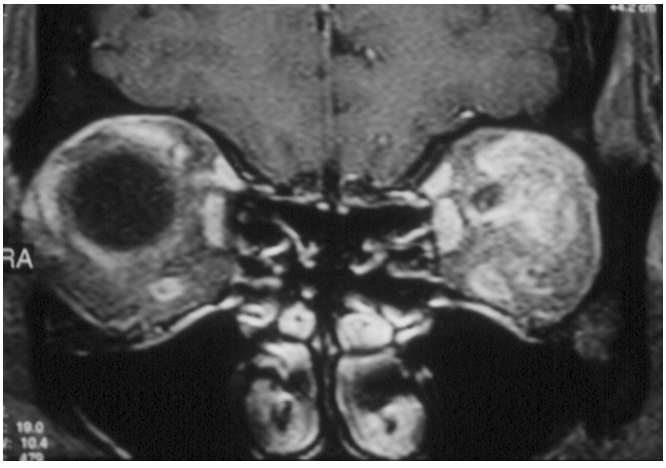

FIGURE 13. Coronal T1-weighted, gadolinium-enhanced orbital magnetic resonance imaging in a patient with acute-onset, painful diplopia and decreased vision in the left eye. The magnetic resonance imaging demonstrates diffuse enhancement of the left orbit consistent with orbital pseudotumor. Symptoms improved with steroid treatment.

Further Diagnostic Considerations

Although uncommon causes of diplopia are not considered in detail elsewhere in this article, 2 specific situations with diplopia as a manifestation deserve mention here, given the potential mortality and morbidity associated with them. These are the onset of diplopia with multiple cranial neuropathies in a diabetic or immunosuppressed patient and intermittent transient episodes of diplopia in an elderly patient. In the first scenario, the importance of screening for invasive fungal disease (such as mucormycosis and aspergillosis) and bacterial cavernous sinus thrombosis cannot be underemphasized. In the second scenario, detailed questioning regarding symptoms of giant cell arteritis, screening with sedimentation rate and c-reactive protein, and low threshold for temporal artery biopsy are essential.

TREATMENT

The various treatments for binocular diplopia are summarized in Table 2.

Occlusion

Occlusion is the quickest and easiest treatment for binocular diplopia, but is the least sophisticated method and completely excludes the possibility of binocularity. Pressure patching 1 eye or taping it shut is a common method used by neurologists in hospital but should be discouraged for at least 2 reasons. First, it is uncomfortable. Second, if the eye opens under the patch or tape, a corneal abrasion or sight-threatening corneal ulcer can develop.

The best method of monocular occlusion uses spectacles. If the patient does not wear glasses, an inexpensive pair of lightly tinted sunglasses can be used. Clip-on occluders are available from opticians and have the advantage of being easily switched from lens to lens. Another good alternative is the use of 3M Transpore frosted plastic tape on the back of 1 lens. Transpore tape is easy to work with and does not leave significant residue when removed from the lens. Cosmetically, it is also very acceptable.

The use of tape also allows the option of partial occlusion. This technique can be very useful in selected cases. For example, some patients with isolated fourth-nerve palsies, thyroid eye disease, or ocular myasthenia can fuse at distance but are diplopic in a reading position or vice versa. In these cases, tape occlusion of the lower half of the lens in front of the paretic eye often works well.

Prism Optics

Fresnel press-on plastic prism optics can be very helpful for patients with binocular diplopia up to 40 prism diopters in magnitude. These prisms are available in 1-diopter increments from 1 to 10 and then in 12, 15, 20, 25, 30, 35, and 40 diopters. I usually place the Fresnel prism in front of the paretic eye and always try to put it on only 1 lens of a patient's glasses to minimize blurring of vision. In certain cases, cutting the prism to fit the lower or upper half of the

TABLE 2. Treatments for Binocular Diplopia

Occlusion
Total: patch, clip-on occluder, tape
Partial: tape
Prisms
Temporary: Fresnel
Permanent: ground-in
Botulinum toxin (BOTOX)
Eye muscle surgery
Eye muscle exercises (orthoptics)
For convergence insufficiency

lens can be done. In patients with a combined horizontal and vertical deviation, a nomogram is available that allows oblique orientation of the prism axis to give both horizontal and vertical power.

Temporary Fresnel prisms are especially useful in patients with cranial nerve palsies because most improve or resolve with time. They are also useful in those with diplopia from thyroid-associated orbitopathy because this group of patients often has diplopia that varies, usually over a period of weeks or months, and the Fresnel prism can be quickly changed as often as needed. Press-on prisms can also be used in ocular myasthenia in selected cases.

Ground-in prisms are useful for stable diplopia problems with deviations of about 12 D or less in primary position.[34] The total power is constrained by optical issues associated with lens design and manufacture. Custom lenses are also available with multiple prisms or prism in only 1 part of the lens. Patients with diplopia limited to downgaze only will benefit from single-vision glasses, high bifocal segments, or a symmetric base-down prism in both lenses to optically elevate the object of regard.[35]

Botulinum Toxin Injections

Botulinum toxin (BTX) injections into selected eye muscles have been used to temporarily treat diplopia resulting from cranial nerve palsies, from thyroid eye disease, and following retinal detachment surgery.[36–39] In general, this treatment should only be performed by an ophthalmologist experienced in orbital injections. The main drawbacks to treatment with BTX are the variability and transience of effect and complications. The most common untoward effects are ptosis, dry eye problems, and worsening the diplopia.[40,41] As a rule, the salutary effects of BTX injection wear off in 3 to 4 months.

Eye Muscle Surgery

Eye muscle surgery is generally reserved for diplopia problems that are longstanding and stable for at least 6 months.[42] Practically, this means diplopia resulting from cranial nerve palsies caused by trauma or tumor and thyroid eye disease.[43] Exceptions can be made if ocular motility is changing rapidly for the worse.[44] Rarely, eye muscle surgery has been used for myasthenic patients with severe ophthalmoplegia and stable signs for at least 5 months.[45]

Eye Muscle Exercises

The use of eye muscle exercises (orthoptics) is limited to the treatment of convergence insufficiency, either the idiopathic variety or that associated with head trauma. This approach is often successful based on our clinical experience and in the experience of others.[46]

CONCLUSIONS

Proper recognition of the potential etiologies of diplopia will permit the practicing neurologist to focus evaluation for each patient. Skilled performance of the ocular motility and ocular alignment examination enhances diagnostic skill and allows for proper treatment of the underlying disorder. The final goal in evaluation and management of a patient with diplopia is eliminating it, and familiarity with the various treatment methodologies for diplopia will facilitate successful diplopia elimination, with minimal interruption of binocular vision.

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