REVIEW ARTICLE

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Approach to Diplopia

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ABSTRACT

PURPOSE OF REVIEW: **"Double vision" is a commonly encountered concern in neurologic practice; the experience of diplopia is always sudden and is frequently a cause of great apprehension and potential disability for patients. Moreover, while some causes of diplopia are benign, others require immediate recognition, a focused diagnostic evaluation, and appropriate treatment to prevent vision- and life-threatening outcomes. A logical, easy-to-follow approach to the clinical evaluation of patients with diplopia is helpful in ensuring accurate localization, a comprehensive differential diagnosis, and optimal patient care. This article provides a foundation for formulating an approach to the patient with diplopia and includes practical examples of developing the differential diagnosis, effectively using confirmatory examination techniques, determining an appropriate diagnostic strategy, and (where applicable) providing effective treatment.**

RECENT FINDINGS: **Recent population-based analyses have determined that diplopia is a common presentation in both ambulatory and emergency department settings, with 850,000 such visits occurring annually. For patients presenting to an outpatient facility, diagnoses are rarely serious. However, potentially life-threatening causes (predominantly stroke or transient ischemic attack) can be encountered. In patients presenting with diplopia related to isolated cranial nerve palsy, immediate neuroimaging can often be avoided if an appropriate history and examination are used to exclude worrisome etiologies.**

SUMMARY: **Binocular diplopia is most often due to a neurologic cause. The onset of true "double vision" is debilitating for most patients and commonly prompts immediate access to health care services as a consequence of functional impairment and concern for worrisome underlying causes. Although patients may seek initial evaluation through the emergency department or from their primary care/ophthalmic provider, elimination of an ocular cause will not infrequently result in the patient being referred for neurologic consultation. A logical, localization-driven, and evidence-based approach is the most effective way to arrive at the correct diagnosis and provide the best outcome for the patient.**

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INTRODUCTION

As with many forms of visual disturbance, the report of "double vision" is entirely subjective and compels the clinician to consider many possible etiologies. Fortunately, a focused history (provided that the reporter is reliable) can often provide a framework for accurately localizing the cause of the diplopia, limiting the differential diagnosis,

and directing the examination toward the underlying pathology. The majority of this article is dedicated to neurologic causes of diplopia with an emphasis on understanding the relevant neuroanatomy subserving ocular motility and providing a framework for interpreting ocular misalignment seen at examination. Armed with this information, the localization of diplopia (to relevant structures of the central nervous system, cranial nerves, neuromuscular junction, extraocular muscles, or orbit) is relatively straightforward and can allow the clinician to develop a viable differential diagnosis, a prudent diagnostic evaluation, and, in some cases, an effective therapeutic strategy to mitigate symptoms.

MONOCULAR DIPLOPIA

Monocular diplopia is defined as the perception of double (or multiple) images when viewing with only one eye. Except in very rare circumstances of bilateral monocular diplopia (eg, cerebral diplopia, polyopia, and palinopsia as manifestations of disease involving the primary or secondary visual cortices[1,2]), the perception of a "shadow," "ghost," "haze," or even an overt "double image" that persists with the nonviewing eye closed is strongly supportive of an ocular cause. Common causes for this include refractive error (uncorrected or outdated correction), corneal defects (including dry eye), cataract, or macular disease.

This can be easily confirmed by placing a pinhole occluder (or similar apparatus) over the viewing eye and asking the patient if this improves or resolves the double vision.[3] If so, the patient should be reassured that he or she does not harbor neurologic pathology and should be referred to an optometrist or ophthalmologist for further evaluation.

While not strictly monocular, it is also helpful for the clinician to be aware of physiologic diplopia, which is a normal perception that can be precipitated by misalignment of the ocular axes when viewing a specific object. For example, focusing on a hand held close to the face will cause objects in the background to appear "double." Likewise, focusing on a distant target and holding an object up close within the field of view will cause a similar phenomenon (ie, "floating finger" or "frankfurter illusion").[4] Concerned patients presenting for evaluation after discovering this phenomenon can be reassured that it is completely natural, and no further investigations are required.

APPROACH TO BINOCULAR DIPLOPIA

Binocular diplopia occurs as a result of misalignment of the eyes/visual axes and, as such, must be regarded as neurologic in etiology. Proper clinical evaluation of binocular diplopia begins with a detailed history with an emphasis on any prior episodes of diplopia, a history of strabismus or "lazy eye" during childhood, and whether the patient has had recent or remote head trauma (CASE 8-1). Perhaps most important is eliciting a detailed description of the patient's perception of the diplopia, including whether the diplopia is constant or intermittent (and any relevant patterns thereof), what the orientation of the diplopia is (that is, whether the relationship between two images is horizontal, vertical, or oblique/diagonal), whether the diplopia is more noticeable at distance or near, and whether the diplopia becomes more (or less) prominent in different directions of gaze. In many cases, accurate localization of the diplopia can be identified by a careful history alone. One recent study found that an effective history and thorough examination accurately identified the cause for the diplopia in the majority (70.5%) of cases, and only a relatively small number (4.7%)

KEY POINTS

- A detailed history and systematic examination can often accurately localize the cause of diplopia.
- Monocular diplopia is rarely due to neurologic pathology.
- Eliciting the orientation of the double image (horizontal, vertical, or oblique), whether diplopia is present at distance or near, and whether the diplopia worsens in any direction of gaze are fundamental to accurate localization.

harbored underlying pathology that required urgent management.[5] Likewise, another study found that for patients presenting to an outpatient facility (representing 95% of the population analyzed), diagnoses were rarely serious, but potentially life-threatening causes (predominantly stroke or transient ischemic attack) were present in 16% of diplopia-related emergency department visits.[6] Such studies highlight the value of an effective strategy for obtaining a relevant history and examination and the utility of using these to guide management.

Intermittent Versus Constant Diplopia

Diplopia that is intermittent tends to either be situation dependent (ie, only noticeable with certain tasks or in specific environments) or worsen with fatigue. The former may suggest a tendency toward ocular misalignment or exacerbating

CASE 8-1

A 64-year-old man presented for evaluation of "double vision" that he had been experiencing for 1 month. He initially noted the double vision while reading his morning newspaper, but over time he became aware of a similar visual disturbance when attempting to descend stairs in his local shopping center.

A detailed history revealed that he did not notice diplopia with other activities. The double image was obliquely oriented and binocular. He stated, "I close one eye when I want to read, and it goes away." The patient did not have eye pain, ptosis, dysphagia, dyspnea, or other neurologic symptoms.

During the interview, the patient relayed that he had been involved in a motor vehicle accident in his thirties, in which he had been "knocked out for a few minutes" but had no other immediate sequelae.

The ocular motility examination revealed a left hypertropia that became more pronounced in right gaze. The patient endorsed diplopia when looking down; when asked to view the junction between the wall and the floor, he reported "seeing two lines, one straight and one diagonal," which, if extended, would intersect to the left. The patient had a head tilt to the right, and review of requested family photographs confirmed that this had been present for many years.

The description of the patient's symptoms, in association with the ocular motility examination and the presence of a long-standing head tilt, was consistent with a posttraumatic left cranial nerve IV palsy with age-related decompensation.

COMMENT

This case exemplifies the utility of eliciting certain characteristics of the diplopia (eg, orientation, presence/absence in specific directions of gaze and with specific activities) in determining a potential localization. It can also be helpful to ascertain whether remote head trauma has occurred and to be attentive to correlating features of a long-standing etiology (such as a head tilt that can be confirmed by photographs). In many cases, patients are able to compensate for ocular misalignment to the extent that they do not notice diplopia for several years until such time as their unrecognized adaptive strategies become decompensated.

elements that are amenable to modification and therefore may eliminate the symptoms. Diplopia that worsens with fatigue immediately raises suspicion for myasthenia gravis (MG) (refer to the section on MG), but it is important to recognize that many other forms of diplopia, such as decompensation of a long-standing strabismus, may also follow this pattern.

Orientation of Images

Binocular diplopia that is horizontal in orientation suggests involvement of the medial or lateral rectus muscle. Diplopia that is vertical and torsional (with the lower image tilted) suggests involvement of the superior oblique muscle (particularly if associated with a compensatory head tilt to the side opposite the weak muscle), while pure vertical diplopia is more likely to reflect brainstem or cerebellar pathology (manifesting as an acquired vertical misalignment of the eyes, referred to as *skew deviation*). Diplopia that is oblique/diagonal, reflecting dysfunction of both vertical and horizontal muscles, suggests dysfunction of the oculomotor nerve (involving some combination of the inferior rectus, superior rectus, and inferior oblique muscles). Further localizing information can be obtained by asking the patient whether the diplopia is worse in a specific direction of gaze (eg, diplopia that is most pronounced at distance and on gaze to the left is supportive of dysfunction of the left lateral rectus muscle/cranial nerve VI).

Additional localizing information can be ascertained by determining if the diplopia is more pronounced at distance or at near. Difficulty with reading or other near tasks suggests dysfunction of convergence, reflecting possible involvement of cranial nerve III or medial rectus muscle or convergence insufficiency. Conversely, if the patient notices diplopia when viewing at distance, dysfunction of divergence should be suspected, prompting further investigation for involvement of the lateral rectus muscle or cranial nerve VI.

Associated Features

Diplopia is always sudden in onset (the perception of double vision is a present or absent phenomenon), although very mild diplopia may be perceived as "blurriness" to some patients; patients and medical personnel often ascribe undue importance to the onset of diplopia as it relates to the potential for a severe underlying cause, and it is appropriate to provide reassurance in this regard. However, consideration of the duration of diplopia (in association with the other historical elements discussed above) can be useful in the elucidation of a differential diagnosis. Additionally, it should be determined whether the patient's diplopia is associated with headache, pain with (attempted) eye movement, ptosis, dysphagia, dyspnea, weakness, or, in patients older than 55 years of age, scalp tenderness, jaw/tongue claudication, fever, chills, unexplained weight loss, or body pain to suggest giant cell arteritis. Diplopia/ocular misalignment that does not change with direction of gaze is classified as comitant and suggests a congenital strabismus (or skew deviation if vertical); diplopia that varies depending on the direction of gaze is termed incomitant (and most often indicates extraocular muscle dysfunction).

Ascertainment of the above historical information is of vital importance. Following this, a schema to discover whether the causative ocular misalignment is due to pathology affecting candidate structures including the brainstem nuclei, cranial nerves, neuromuscular junction, extraocular muscles, or orbital tissues can be employed (FIGURE 8-1[7]) based on supportive findings at the neurologic examination.

KEY POINTS

- **Diplopia that occurs with fatigue does not necessarily imply myasthenia gravis; long-standing and decompensated ocular misalignment can also become symptomatic when patients are tired or under stress or in the setting of concomitant illness.**
- **Diplopia/ocular misalignment that does not change with the direction of gaze is classified as comitant; diplopia that varies depending on the direction of gaze is termed incomitant and most often indicates extraocular muscle dysfunction.**

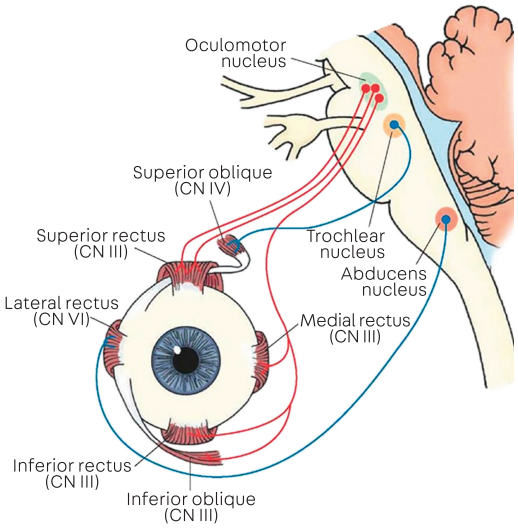

FIGURE 8-1
Innervation of the muscles of the eye. Origin and distribution of the cranial nerves and their respective innervation of the extraocular muscles.
CN = cranial nerve.
Reprinted from *what-when-how.com/neuroscience*.[7]

Examination

Detailed examination of the ocular motor system is straightforward and time efficient and does not require sophisticated diagnostic instrumentation. Additionally, evaluation of eye movements is not perceived as threatening (even to the most apprehensive patient), and aspects of clinically relevant dysfunction can be ascertained even in patients who are unable to fully participate. Key components of the ocular motility examination include fixation/gaze holding, monocular eye movements (ductions), and assessment of binocular eye movements (versions, pursuits, and saccades).

Initially, fixation should be evaluated by asking the patient to view a target of visual interest (the large letter on an eye chart at distance or the "95" at the top of a near card) in primary viewing position. Careful attention should be paid to any instability of fixation, which may include square-wave jerks (spontaneous, small-amplitude horizontal saccades away from fixation followed promptly by a corrective saccade in the opposite direction [note that square-wave jerks occurring fewer than 9 times per minute can be normal in most individuals]) or nystagmus, which may suggest pathology affecting ocular coordination (**VIDEO 8-1**).

Next, evaluation of ductions is completed by occluding one eye and asking the patient to follow a visual target through all cardinal gaze positions (**VIDEO 8-2**). Assessment should be made of any apparent limitation or restriction of eye movements; additionally, the pursuit movements (ie, tracking) should be smooth and uninterrupted. Examination of fixation is commonly overlooked during the ocular motility examination but is essential in identifying potential pathologic features that may be associated with diplopia. Subtle asymmetry in ocular alignment is sometimes easer to discern with testing of versions, in which the same process is repeated but with both eyes viewing (thereby allowing for comparison of symmetry between the two eyes simultaneously) (**VIDEO 8-3**).

Finally, testing of saccades involves asking the patient to rapidly and alternately fixate on two different targets (eg, a finger held eccentrically and the examiner's nose in primary gaze). This should be performed in both the horizontal and vertical planes (**VIDEO 8-4**). In addition to noting any apparent ocular misalignment, consideration should be given to any delay in initiation, the velocity of the saccades, and any inaccuracy (ocular dysmetria) as a potential indicator of brainstem or cerebellar dysfunction that may accompany the diplopia.

Diagnostic Evaluation

In the setting of trauma, and particularly with any indication of restricted ocular motility, CT of the skull bones may be indicated. In all nontraumatic cases, MRI (with dedicated skull base and orbital imaging) is preferable to CT. When cranial nerve dysfunction is suspected, care should be taken to directly review the images and "follow the course" of the involved cranial nerve from its origin to identify structural pathology. If other signs or symptoms of increased intracranial pressure are present, it is also important to visualize the brain parenchyma to exclude space-occupying lesions. In general, neuroimaging has a low diagnostic yield in isolated fourth, pupil-sparing third, and sixth nerve palsies in older patients with vascular risk factors. However, in one study, 10% of patients older than 50 years of age with one vascular risk factor were found to have other causes, including neoplasm, infarction, and giant cell arteritis.[8] Other disease-specific considerations related to the diagnostic evaluation are included below.

CAUSES OF BINOCULAR DIPLOPIA

A thorough evaluation of ocular motility allows the examiner to consider the various potential causes of ocular misalignment, which can be broadly localized to supranuclear, internuclear, infranuclear, neuromuscular junction, extraocular muscle, or orbital dysfunction. A systematic and stepwise approach to considering the relative likelihood of each of these neuroanatomic locations is helpful in the clinical setting.

Dysfunction of Supranuclear and Internuclear Ocular Motor Control

It is important to remember that the intracranial apparatus responsible for directing and coordinating ocular motility (and thereby ensuring single vision) is complex. Therefore, while more distal pathologies that cause diplopia (eg, isolated cranial nerve palsies, disorders of the neuromuscular junction, and orbital restrictive processes) can be straightforward, more proximal lesions may be difficult for the practicing neurologist to precisely localize in the setting of a single examination. Lesions affecting the cortical connections to the nuclei of II, IV, and VI are termed *supranuclear*; lesions affecting the connections between nuclei are *internuclear*; and those affecting the nerves, neuromuscular junction, or muscles are *infranuclear*.

Broadly considered, dysfunction of the cerebral hemispheres (precipitated by metabolic disorders or medications); neurodegenerative diseases that compromise the basal ganglia (such as the parkinsonian syndromes and Huntington disease); or structural injury to the pons, midbrain, or cerebellum are all potential causes of (or contributors to) diplopia. Each of these, however, will be accompanied by other neurologic signs and symptoms, often more prominent than the diplopia itself, that will provide helpful diagnostic information.

However, important considerations within this category that may present with isolated diplopia include skew deviation and internuclear ophthalmoplegia (INO). Skew deviation results in vertical ocular misalignment/diplopia that typically results from injury to the utricular-vestibular-ocular pathway (brainstem or cerebellum) governing vertical and torsional eye position in response to body tilt. It is similar in presentation to cranial nerve IV palsy but can be differentiated by its propensity for the vertical misalignment to decrease by 50% or more when the patient is measured in the supine position as compared to

KEY POINTS

- **Assessment of fixation is commonly overlooked during the ocular motility examination but is essential in identifying potential pathologic features that may be associated with diplopia.**
- **Neuroimaging has a low diagnostic yield in isolated fourth, pupil-sparing third, and sixth nerve palsies in older patients with vascular risk factors. However, a small number of patients older than 50 years of age may have other causes including neoplasm, infarction, and giant cell arteritis.**
- **While the localization of isolated diplopia can be relatively straightforward, the complex nature of ocular motility and coordination makes them susceptible to disruption by more diffuse cerebral dysfunction.**

CASE 8-2

A 34-year-old man presented for evaluation of visual distortion, which he had noticed in the past week when watching his daughter's youth tennis tournament. He reported that when watching her serve the ball from the right side of the court to the left, he would see "two tennis balls for a second, and then things went back to normal." He did not report any other occasions of double vision, nor did he endorse eye pain, ptosis, or other neurologic symptoms.

Testing of saccades confirmed a right internuclear ophthalmoplegia with otherwise normal ocular motility and alignment. Given the patient's age and otherwise unremarkable examination, brain MRI was required to evaluate for a demyelinating lesion involving the medial longitudinal fasciculus (MLF). Given the patient's report that the symptom manifested later in the day, ocular myasthenia gravis (MG) was also considered. (Patients with MG may develop dyscoordinated eye movements that can mimic a lesion of the MLF, known as *pseudointernuclear ophthalmoplegia*.)

MRI of the brain disclosed an enhancing lesion involving the right MLF, in addition to other characteristic lesions of multiple sclerosis within the brain parenchyma. He was treated with a 3-day course of IV steroids, and the ocular motility disturbance resolved within 6 weeks.

COMMENT

This case highlights a common description of patients with internuclear ophthalmoplegia, a transient perception of two images that "have to catch up with each other." Although this cause of diplopia may be associated with failure of adduction on smooth pursuit testing, in certain cases pursuit appears normal, and saccadic testing is needed to make the diagnosis (showing a delay in adduction). Given that the predominant feature of myasthenia gravis is worsening with fatigue, patients who are symptomatic later in the day or when tired should be evaluated for neuromuscular junction disease.

TABLE 8-1 Innervations and Actions of the Ocular Motor System

Cranial Nerve	Muscle	Action
III (Superior branch)	Superior rectus	Elevation, intorsion, adduction
III (Inferior branch)	Medial rectus	Abduction
	Inferior rectus	Depression, extorsion, adduction
	Inferior oblique	Extorsion, elevation, abduction
IV	Superior oblique	Intorsion, depression, abduction
VI	Lateral rectus	Adduction

the upright position.[9] INO presents with horizontal diplopia that may be characterized by brief, specific exacerbations; patients often describe a sense of "one eye catching up to the other" with horizontal saccades. Key examination findings are slowed adduction in one eye with corresponding abducting nystagmus in the other eye (these findings are most often best ascertained by testing saccades, as discussed above). INO can sometimes be mistaken for third nerve palsy, but the ocular motility examination can exclude this based on absent involvement of other muscles innervated by the third nerve (superior rectus, inferior rectus, and levator among them). Therefore, a key examination feature that helps distinguish INO from medial rectus muscle weakness or a partial third nerve palsy is that adduction with convergence is preserved. INO results from the dysfunction of the medial longitudinal fasciculus, which connects the ipsilateral sixth nerve nucleus in the pons to the contralateral third nerve nucleus (medial rectus subnucleus) in the midbrain. Although several possible causes exist, the most frequently encountered are demyelination (in patients younger than 50 years of age) and brainstem stroke (in patients older than 50 years of age). Because of the potential causes of both skew deviation and INO, neuroimaging (preferably brain MRI) is indicated for patients presenting with these findings. It is also important to remember that INO may be bilateral; these lesions often occur in the midbrain and affect the convergence nucleus, resulting in a large-angle exotropia (meaning the eyes are deviated outward) and convergence insufficiency (the so-called wall-eyed bilateral INO) (CASE 8-2).

KEY POINT

- Internuclear ophthalmoplegia is best identified by testing saccades.

Dysfunction of Nuclear and Infranuclear Ocular Motor Control

The oculomotor (third), trochlear (fourth), and abducens (sixth) cranial nerves are the final mediators of the complex mechanism of ocular motility that originates in the brainstem, with modulation from the frontal eye fields, cerebellum, and other structures within the brain. Failure of these nerves to orient the globes in a coordinated fashion, even to a mild degree, will result in the perception of double vision (or, if subtler, "blurred vision" that resolves when the patient occludes either eye). Principal actions of these cranial nerves are reviewed in TABLE 8-1, but as a practical matter, it is helpful to remember that cranial nerve VI (innervating the lateral rectus muscle) abducts the eye, cranial nerve IV (innervating the superior oblique muscle) depresses and intorts the eye for actions such as reading and negotiating curbs/going down stairs or escalators/addressing golf balls, and cranial nerve III does "everything else."

A thorough understanding of the patterns and causes of diplopia related to cranial nerve dysfunction is of vital importance to the clinician when it comes to evaluating diplopia. As evidence of this, a study by O'Colmain and colleagues[5] found that of 149 patients presenting with diplopia of fewer than 4-weeks duration, more than 50% had an isolated third, fourth, or sixth cranial nerve palsy; the remainder of the patients were determined to have a mechanical cause (10.7%), a dysfunction of higher cortical control (10.1%), decompensation of a preexisting ocular misalignment (8.1%), an idiopathic cause (6.7%), or a monocular cause (5.4%).

Adding to the localizing information that can be gleaned from dysfunction of the third nerve is the possibility of levator involvement (resulting in ptosis) or involvement of the pupil (resulting in anisocoria due to mydriasis of the involved eye) caused by disruption of the central caudal nucleus (a midline, unpaired structure, one of the third nerve nuclei responsible for innervation of the bilateral

levator palpebrae muscles) or Edinger-Westphal nucleus (or their axons), respectively. When the palsy results from injury to the third nerve nucleus on one side, the patient may present with ptosis and supraduction weakness in the eye contralateral to the more complete third nerve palsy because of bilateral innervation by the central caudal nucleus and decussation of fibers from the superior rectus nucleus. If, instead, the fascicles of the third nerve are affected as they course through the midbrain, patients may present with diplopia that is accompanied by ataxia, tremor, or hemiparesis. The discovery of a new pupil-involving third nerve palsy should prompt a search for a compressive

CASE 8-3

A 64-year-old man presented for evaluation of binocular horizontal diplopia that began 2 weeks earlier and was most bothersome when viewing at a distance and when driving. He noted that the diplopia was more prominent when he directed his gaze to the left but otherwise it was present "all the time." He had a history of hypertension, diabetes mellitus, and dyslipidemia.

On examination, the patient's left eye did not fully abduct, but all other movements were intact. Alternate cover testing identified an esodeviation (or "in-turning" of the eyes) that was minimal in right gaze but increased in left gaze. The fundus examination was normal, without optic disc edema.

Given the patient's history of hypertension, diabetes mellitus, and dyslipidemia, his presentation was consistent with microvascular cranial nerve VI palsy. No other cranial nerve palsies were evident, and the remainder of the neuro-ophthalmic examination was normal (with specific regard to papilledema or other features to suggest elevated intracranial pressure). A restrictive process within the orbit (causing restriction of the medial rectus muscle) was also a possibility, but the absence of abnormal eyelid findings, pain with eye movements, or proptosis made this less likely. Although the patient was older than 55 years of age, giant cell arteritis was not supported due to the paucity of systemic symptoms. Appropriate modification of cerebrovascular risk factors was recommended.

The patient returned for follow-up 8 weeks later, at which time he volunteered that the "double vision is gone, except when I look all the way to the left." Ocular motility had improved, and the reduced abduction of the left eye was virtually resolved. Neuro-ophthalmic follow-up continued for another month, at which time the ocular motility examination was normal and diplopia had fully resolved.

COMMENT

This case highlights the importance of determining the pattern of the ocular misalignment. Binocular horizontal diplopia that is worse at distance and in left gaze is consistent with impairment of divergence and suggests involvement of the left lateral rectus muscle/cranial nerve VI. Given the potential for increased intracranial pressure to present with a sixth nerve palsy as a false localizing sign, a fundus examination should be performed to evaluate for papilledema, and consideration should be given to neuroimaging to exclude a space-occupying lesion.

lesion, specifically an aneurysm of the posterior communicating artery. In patients older than 50 years of age, third nerve palsies that spare the pupil but are otherwise complete are frequently the result of ischemia, and patients tend to recover in approximately 3 months.

Isolated fourth nerve palsies are frequently the result of trauma but also may reflect decompensation of a congenital dysgenesis of the nerve or superior oblique muscle.

Isolated sixth cranial nerve palsies (CASE 8-3) may be falsely localizing given that the protracted course of the nerve from the pontomedullary junction, along the clivus, then piercing the dura at the Dorello canal, over the petrous ridge, and finally into the cavernous sinus, makes it especially susceptible to disruption via stretching of the nerve caused by increased intracranial pressure. Therefore, patients presenting with diplopia due to cranial nerve VI palsy should be carefully evaluated for papilledema or other features suggestive of intracranial structural pathology.

KEY POINTS

- Patients presenting with cranial nerve VI palsy should be evaluated for signs and symptoms of increased intracranial pressure, which includes fundus examination.
- Myasthenia gravis can mimic any pupil-sparing ocular motility deficit.

Dysfunction of the Neuromuscular Junction

MG is an autoimmune disease in which circulating antibodies block the effective communication between the neurotransmitter acetylcholine and its receptors on the postsynaptic membrane. While generalized forms of the disease exist and patients with ocular MG may progress to generalized MG,[10] intermittent diplopia and ptosis remain the predominant presenting symptoms.

A long-regarded clinical rule of thumb is that ocular MG can mimic any pupil-sparing cause of diplopia, and thus this should be considered within the differential for most patients presenting with isolated diplopia. The primary historical feature that should prompt consideration of MG, however, is the intermittency of the double vision and its tendency to occur with fatigue and resolve with rest. This can be easily demonstrated during the examination by noting any abnormalities in ocular motility and by careful measurement of ocular misalignment, then repeating the same portions of the examination after asking the patient to rest (or sleep) with his or her eyes closed for 30 minutes or following the application of ice to the closed eyes for 2 minutes (the ice pack test).[11,12] Improvement in the examination under these conditions is highly suggestive of MG; recrudescence of the findings over a short period of time thereafter is also supportive.

Additionally, patients and their family members should be queried about potential associated symptoms such as ptosis (which is also commonly variable and more prominent with fatigue), dysphagia, dyspnea, or other symptoms of generalized neuromuscular junction dysfunction. In addition to the symptoms improving with rest and worsening with fatigue, which can be demonstrated during the examination, additional ocular findings can assist with clinical confirmation. These findings include eyelid curtaining (lifting of one eyelid by the practitioner causes the fellow eyelid to droop), the Cogan eyelid twitch sign (in which the upper eyelid jerks up once or twice upon return to primary gaze from downgaze, especially if following a prolonged period of upgaze),[13] and weakness of the orbicularis muscles with forced or prolonged eye closure.

Serum testing for acetylcholine receptor (AChR) antibodies can be helpful in confirming autoimmune MG but is positive in only 50% to 70% of patients with purely ocular disease.[14] Approximately half of patients with clinical features of MG but who are negative for the AChR antibody may harbor antibodies to muscle-specific tyrosine kinase (MuSK).[15] These patients are likely to have a

distinct constellation of features including prominent bulbar weakness and may worsen when treated with acetylcholinesterase inhibitors.[16] Anti–lipoprotein receptor–related protein 4 (LRP4) antibody has been reported in approximately 10% of patients who are negative for both anti-AChR and anti-MuSK antibodies,[17] but the presence of LRP4 antibodies is widely variable based on a number of factors.[18] Nerve conduction testing looking for a decrement on repetitive nerve stimulation or assessing for jitter on single-fiber EMG[19] can be used in equivocal cases but is often relegated to patients with symptoms of systemic disease. In patients with pure ocular MG, single-fiber EMG of the orbicularis oculi is more sensitive than repetitive nerve stimulation.[20] Treatment for ocular MG is varied and principally relies on inhibition of the metabolism of acetylcholine (pyridostigmine) or modulation of the immune system (steroids or other immunomodulatory therapies).

Orbital Disease

Various pathologic processes within the orbit can impair the normal contraction of the extraocular musculature or mechanically restrict the movement of the globe. Thyroid ophthalmopathy (also referred to as thyroid eye disease or Graves ophthalmopathy) is an autoimmune disease that causes progressive edematous changes of the orbital musculature resulting in restriction of eye movements. The inferior rectus muscles are most commonly involved, followed by medial and superior rectus muscles[21]; diplopia is most commonly vertical as the lateral rectus muscles are less likely to be involved. Because of progressive enlargement of the extraocular muscles, proptosis and periorbital edema, which tends to be more pronounced on awakening and improves during the course of the day, are associated features. Most important, progressive muscle enlargement may cause compression of the optic nerve at the orbital apex; for this reason, formal visual field studies are required to monitor for insidious visual field constriction. Diagnosis can be confirmed by imaging (CT or MRI) of the orbits documenting characteristic edema and hypertrophy of the extraocular muscles; laboratory studies for thyroid dysfunction may or may not be abnormal, but measurement of thyroid-stimulating hormone (TSH) receptor antibodies can correlate with disease severity and help monitor for response to treatment.[22] In the absence of severe symptoms or impending visual decline, most patients can be managed conservatively with a focus on treating underlying thyroid dysfunction (if present), mitigating corneal exposure related to proptosis, and discontinuation of smoking. Moderate disease can be treated with immunomodulation (typically oral prednisone); severe disease may require surgery for orbital decompression. More recently, an insulin-like growth factor I receptor (IGF-IR) inhibitor (teprotumumab) has been shown to improve proptosis and produce rapid symptomatic improvement as compared to placebo.[23]

Idiopathic orbital myositis, also known as idiopathic orbital inflammation, is a rare inflammatory disorder resulting in painful, isolated extraocular muscle dysfunction most commonly in the distribution of the third cranial nerve. It is more likely to occur in women and in the third decade of life.[24] Horizontal diplopia with the presence of pain is central to the diagnosis; proptosis, periocular edema, and conjunctival hyperemia may also be present. The diagnosis is confirmed by MRI of the orbits documenting unilateral thickening and enhancement of the involved muscle and its myotendinous insertion.[25] Similar orbital inflammation can be seen in IgG4-related disease, an immune-mediated fibro-inflammatory

condition with potential effects on multiple structures (including the orbits); screening for elevation of serum IgG4 should be considered. Orbital lymphoma may appear similar to idiopathic orbital inflammation and should be considered in progressive or recurrent cases, especially in older patients. For patients with idiopathic orbital myositis–associated diplopia, systemic corticosteroids with a protracted taper is the principal form of treatment; a more thoughtful algorithm for management of this disorder has been proposed.[26]

TREATMENT APPROACH

Ideally, resolution of the underlying cause of the diplopia is achieved. However, depending on the etiology, this may require time for the therapeutic intervention to take effect. In other circumstances, such as with patients harboring a decompensated strabismus or stroke, the diplopia may remain.

Generally speaking, long-standing or residual diplopia can always be resolved. Careful consideration should be given to which therapeutic strategy is most satisfactory, will provide the greatest return to the desired functional status, and is consistent with the patient's concomitant conditions and long-term goals.

Monocular Occlusion

For patients with binocular diplopia, the most straightforward approach is covering one eye. Many patients will recognize this independently and may unconsciously close one eye to improve their visual experience. On a longer-term basis, this can be achieved through the use of an eye patch, although some patients may eschew this given the cosmetic implications. Moreover, it is crucial to instruct patients using an eye patch to ensure that the eyelid under the patch is fully closed to minimize the potential for corneal injury. For similar reasons, this method should be avoided for any patient with impaired corneal sensation (eg, because of concomitant cranial neuropathy or other causes). A more acceptable approach is to place translucent tape over one lens of the patient's spectacles; some patients prefer to fashion a fabric cover that they place over the frame of one lens. Patients should be assured that occlusion of either eye will mitigate the diplopia, but care should be taken to ensure that the better-seeing eye is not covered. They should also be informed that this method will disrupt binocular vision as it relates to depth perception, so care should be taken when driving or when engaging in other potentially hazardous tasks.

Prism Lenses

For patients who wear spectacles, a prism lens can be applied to one or both lenses to "bend" the disparate images into single vision. This is most effective for patients with comitant and relatively small-angle ocular misalignment; for other patients this may still be beneficial, but the expectation should be for single vision in primary position (as the prism will not mitigate the incomitant ocular misalignment in all directions of gaze simultaneously). Ideally, a Fresnel (temporary) prism is applied, and the patient is asked to determine over a period of days to weeks whether the prism is effective. This allows for easy adjustment of the prism strength based on the patient's experience or in the event that the degree of ocular misalignment changes, such as with an improving microvascular cranial nerve VI palsy. Once the appropriate prism strength is confirmed, this can be "ground in" to a pair of spectacles for full-time wear.

KEY POINTS

- Antibody and electrophysiologic testing for myasthenia gravis may be supportive, but this remains a primarily clinical diagnosis.
- Patients with known or suspected thyroid ophthalmopathy should have periodic monitoring with formal visual fields because of the possibility of peripheral vision constriction by compression of the optic nerves as a consequence of enlarging extraocular muscles.
- For patients with new-onset (eg, microvascular) or transient (eg, myasthenia gravis–related) diplopia, monocular occlusion for mitigation of symptoms is immediately effective and can be employed as needed when symptoms are present.

KEY POINT

● **Prism correction is useful for patients with stable or comitant ocular misalignment; eye alignment surgery is useful for patients with incomitant diplopia.**

Eye Alignment Surgery

For patients with large-angle, incomitant ocular misalignment that is not amenable to (or has failed) prism correction, surgery to reposition the extraocular muscles with the goal of "realigning the eyes" may be beneficial. Of note, surgical intervention for diplopia related to MG is rarely recommended as a consequence of the intermittent and variable nature of the ocular misalignment and the potential for complete recovery with medical therapy.

CONCLUSION

Diplopia of any pattern or degree is disconcerting to patients and often provokes consternation for the evaluating clinician. However, a systematic approach that relies on a careful history to elucidate candidate sites of localization (brainstem/nuclear, cranial nerve, neuromuscular junction, muscle), followed by precise examination techniques to support the most likely etiology, allows for accurate bedside diagnosis in most cases. It is on this basis that the potential for worrisome underlying etiologies can be evaluated and confirmatory diagnostic studies can be judiciously directed.

Finally, it is often very comforting for patients to know that diplopia (in most instances) is not associated with pathology that will cause overt vision loss. Furthermore, although the elimination of the underlying cause (if possible) is ideal, the symptom of double vision can always be mitigated. Interventions range from simple monocular occlusion to eye alignment surgery, but the patient need not expect that long-term resolution is in question.

VIDEO LEGENDS

VIDEO 8-1
Examination of fixation. The patient is asked to maintain focus on a visual target (the "big 95" at the top of a Rosenbaum Vision Screen is preferred). The examiner should note the patient's ability to maintain stability of gaze, paying particular attention to square-wave jerks, other saccadic intrusions, or nystagmus.

VIDEO 8-2
Examination of ductions. One of the patient's eyes is covered, and with the other eye, he is asked to follow a visual target slowly through the cardinal positions of gaze.

VIDEO 8-3
Examination of versions. The patient is asked to follow a target through the cardinal positions of gaze while viewing it with both eyes. The examiner should note whether ocular pursuit movements are smooth and controlled; this also allows for any asymmetry between the degree of movement of each globe compared to the other to be noted.

VIDEO 8-4
Examination of saccades. The patient is asked to maintain fixation on a central target, then to rapidly direct his gaze to an eccentric target, then back to central fixation. This should be performed in both the horizontal and vertical planes.

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