CHAPTER 18

Diplopia

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PERSPECTIVE

Epidemiology

Diplopia, or double vision, is of two types, monocular and binocular. For patients who present to the emergency department (ED) with diplopia, most cases are binocular, with cranial nerve (especially sixth nerve) palsies being among the most common causes. The remainder (≈15%) are monocular.

Pathophysiology

Monocular diplopia, or double vision that persists in one affected eye, even with the other one closed, is an ophthalmologic problem related to distortions in the light path. Binocular diplopia, or double vision that resolves when either eye is closed, is the result of a misalignment in the visual axes and has a wide range of causes. These can be organized in a progression from the eye distally to the brainstem proximally. The process responsible might involve oculomotor muscle dysfunction, cranial nerve (CN) dysfunction, or intranuclear or supranuclear lesions in the brainstem or above. In a recent, prospective observational study of 260 ED patients presenting with binocular diplopia, a secondary cause of the diplopia was delineated in 36% and, of these, the most frequent diagnoses were stroke (45%), multiple sclerosis (18%), brain tumors (12%), and cerebral aneurysms (8%).[1]

DIAGNOSTIC APPROACH

Differential Considerations

The causes of diplopia are myriad, ranging from relatively benign to significantly pathologic. The clinical approach in the ED entails sorting out those that may result in rapid and profound morbidity from those that are less acute. Table 18.1 outlines some key causes of diplopia prioritized by immediate acuity, with mechanism and distinguishing features.

Binocular diplopia may be due to a mechanical orbitopathy, a palsy of one or more of the oculomotor cranial nerves, a proximal neuroaxial process involving the brainstem and related cranial nerves, or a systemic neuromuscular process.

Monocular diplopia is an ophthalmologic problem related to distortions in the light path from dry eyes, a corneal irregularity, cataract or lens dislocation[2] or, rarely, from retinal wrinkles involving the macula.

A restrictive mechanical orbitopathy can be caused by orbital myositis, trauma, or infection (abscess), or from craniofacial masses, any of which can directly restrict movement of a single eye. A restrictive orbitopathy is identified by characteristic symptoms and signs combined with the absence of any other focal neurologic deficits. Often involving only a single extraocular muscle, orbital myositis may be a manifestation of a variety of steroid-responsive conditions such as Wegener's granulomatosis, giant cell arteritis, systemic lupus erythematosus, dermatomyositis, sarcoidosis, rheumatoid arthritis, or idiopathic orbital inflammatory syndrome (orbital pseudotumor).

Graves' orbitopathy is the most common cause of ocular myopathy in older adults, will affect at least 50% of patients with Graves' disease,[3] and is bilateral in at least 85% of cases. The patient presenting with thyroid-related diplopia will likely have a preexisting diagnosis of Graves' disease, but may present with isolated diplopia prior to the onset of systemic symptoms (and diagnosis).[3]

The oculomotor (CN III), trochlear (CN IV), and abducens (CN VI) cranial nerves innervate the muscles that move the eye. With regard to an oculomotor cranial nerve palsy, CN VI is the most commonly affected, followed by CN III, and then CN IV.[2] An isolated simple mononeuropathy in CN III, IV, or VI may be from a demyelinating process (eg, multiple sclerosis[4]), hypertensive or diabetic vasculopathy, or compression. Each nerve has characteristic predilections to which it is vulnerable. In adults, CN III is usually affected by diabetic or hypertensive vasculopathy. Aneurysms in the posterior communicating (most common), basilar, superior cerebellar, posterior cerebral, and cavernous internal carotid arteries are a close second.[5] CN IV is usually affected by trauma from abutting against the tentorium, typically not an isolated symptom or finding, followed by vascular causes. Due to its length, CN VI is the most common nerve to be affected by tumors, elevated intracranial pressure, and microvascular ischemia.[6]

A cavernous sinus infection, mass, or vasculitis may affect CN III, IV, and VI simultaneously (orbital apex syndrome), but typically affects CN VI first because it traverses through the cavernous sinus, as opposed to within its wall, like CNs III and IV. Causes include carotid-cavernous fistula, inflammatory vasculitides such as giant cell arteritis, Tolosa-Hunt syndrome (a rare idiopathic vasculitis), or tumor or infiltration (eg, lymphoma, sarcoidosis) in the orbital apex.[7] A complex palsy in the cavernous sinus may also be iatrogenic due to intravascular injection or diffusion of anesthetic along tissue planes into the pterygoid venous plexus from an intraoral dental anesthetic nerve block.[8] Herpes zoster ophthalmicus is a well-described cause of orbital apex syndrome.[9-11]

A focal brainstem lesion may be from multiple sclerosis (as a clinically isolated syndrome, of which 68% manifest as diplopia).[4] A more diffuse but localized brainstem process may be caused by brainstem tumor, brainstem lacunar stroke,[2] impending basilar artery thrombosis, vertebral artery dissection, or ophthalmoplegic migraine.[3] A vertebral artery dissection may present with diplopia alone, as can an impending basilar artery thrombosis, which can also result in a coma.[12]

A more diffuse process involving the brainstem and/or CNs III, IV, and VI may be infectious, autoimmune, neurotoxic, or metabolic, and involve other neurologic structures, resulting in additional symptoms and signs. Possibilities include basilar meningoencephalitis (cryptococcal,[13] carcinomatous, or viral[14]), at times with the diplopia being the only symptom,[15] botulism,[16] an autoimmune process such as Miller-Fisher or Guillain-Barré syndrome,[17] and Wernicke's encephalopathy, in which the ophthalmologic manifestations are due to metabolically induced lesions in the pontine tegmentum, abducens nucleus, and oculomotor nucleus.[18]

TABLE 18.1

Important Causes of Diplopia

DIPLOPIA-CAUSING ENTITY	MECHANISM AND MORTALITY	DISTINGUISHING FEATURES
TIER 1—CRITICAL		
Basilar artery thrombosis	Impending thrombosis of the basilar artery with brainstem ischemia; untreated mortality, 70%–90%	Vertigo, dysarthria, other cranial nerve involvement; risk factors for stroke
Botulism	Toxin inhibits release of acetylcholine at cholinergic synapses and presynaptic myoneural junctions; untreated mortality, 60%	Dysarthria, dysphagia, autonomic dysreflexia, pupillary dysfunction
Basilar meningitis	Infection; untreated mortality, close to 100% if bacterial (15%–20% if treated)	Headache, meningismus, fever
Aneurysm	Enlarging aneurysm directly compresses cranial nerve; untreated rupture risk = 1%/yr (3.5%/yr for previously ruptured); mortality, 26%–67%/rupture	CN III palsy with pupillary involvement
TIER 2—EMERGENT		
Vertebral dissection	Dissection causes vertebrobasilar ischemia; acute untreated mortality, 28% (2%–5% if neurologically asymptomatic)	Neck pain, vertigo; risk factors for vertebral dissection
Myasthenia gravis	Autoantibodies develop against acetylcholine (ACh) nicotinic postsynaptic receptors; untreated crisis mortality, 42% (5% if treated)	Fluctuating muscle weakness, ptosis, and diplopia worsen with activity, improve with rest
Wernicke's encephalopathy	Thiamine-dependent metabolic failure and tissue injury; untreated mortality, 20%	Nystagmus, ataxia, altered mental status, ophthalmoplegia; alcoholism and nutritional deficiency
Orbital apex syndrome, cavernous sinus process	Inflammation or infection in the orbital apex or cavernous sinus directly affects oculomotor cranial nerves; acute mortality low unless infectious and complicated by meningitis	Combination of palsies of CN III, IV, or VI, with retro-orbital pain, conjunctival injection, possible periorbital, facial numbness
TIER 3—URGENT		
Brainstem tumor	Tumor involvement at the supranuclear level; acute mortality low (long-term mortality variable)	Skew deviation—vertical diplopia, internuclear ophthalmoplegia
Miller-Fisher syndrome	Autoantibodies develop to a cranial nerve ganglioside, GQ1b; acute mortality low (if fully differentiated from GBS; mortality, 2%–12% if GBS)	Ophthalmoplegia, ataxia, areflexia
Multiple sclerosis	Demyelinating lesions; acute mortality low	Internuclear ophthalmoplegia
Thyroid myopathy (Graves' disease)	Autoimmune myopathy; acute mortality low in regard to ocular complaints	Proptosis, restriction of elevation and abduction of the eye, signs of Graves' disease
Ophthalmoplegic migraine	Inflammatory cranial neuropathy; low mortality, self-limited disease	Ipsilateral headache, CN (usually III) palsy
Ischemic neuropathy	Microvascular ischemia; mortality low, self-limited disease	Isolated CN palsy (pupil-sparing if CN III)
Orbital myositis, pseudotumor	Autoimmune or idiopathic myositis; acute mortality low in regard to ocular complaints	Eye pain, restriction of movement, periorbital edema; exophthalmos and chemosis when more severe
Orbital apex mass	Tumor, infiltration, or mass effect in orbital apex or cavernous sinus directly compresses oculomotor cranial nerves; acute mortality low	A combination of palsies of CN III, IV, or VI and possible periorbital, facial numbness, with retro-orbital pain, proptosis, signs of venous congestion

Snake envenomations and tick paralysis can, on rare occasions, present with isolated diplopia, with diplopia being an early and frequent manifestation of neurotoxicity from certain snake venoms.[19] Diplopia may also be part of a paraneoplastic syndrome, but the prototypical neuromuscular cause of diplopia is myasthenia gravis. The initial symptoms are ocular in 85% of myasthenia cases, due to diplopia in 14% of cases. In addition, the symptoms of myasthenia gravis are solely ophthalmologic in almost 20% of patients.[20] However, patients with myasthenia will typically present with diplopia in the setting of a preestablished diagnosis, which facilitates a determination, if not immediate recognition, of the cause.

Pivotal Findings

There are four aspects of questioning that help formulate the differential diagnosis in diplopia: (1) timing of onset and symptoms; (2) directionality and orientation of the diplopia; (3) presence of pain; and 4) presence of other associated symptoms.[2] In terms of the timing of onset, a truly sudden onset suggests an ischemic cause, cerebrovascular or microvascular, especially if the intensity or degree of diplopia was maximal at onset. A fluctuation of symptoms over time may suggest transient ischemic attacks or an impending stroke, but more generally implies a neuromuscular disease.[2] Regarding the directionality of the diplopia, the

directions of gaze that elicit or worsen the diplopia and the general orientation of that diplopia—that is, horizontal, vertical, torsional—should be carefully determined to localize the problem. Finally, symptoms associated with the diplopia (eg, pain, neurologic or neuromuscular symptoms) are critical to forming a differential diagnosis, if not making the diagnosis. The presence of pain suggests an inflammatory or infectious process and narrows the differential significantly.

The patient complaining of diplopia should have a thorough neurologic examination, with attention to the cranial nerves and an evaluation of the six cardinal movements of gaze. Each extraocular muscle (and the nerve that supplies it) has a maximal action in a specific direction, and the evaluation of gaze should therefore specifically follow the configuration of a six-limbed asterisk, or an H (Fig. 18.1). The patient should also undergo a careful pupillary and facial examination, looking for signs of pupillary asymmetry, ptosis, lid lag, conjunctival injection or chemosis, periorbital swelling, or proptosis and overall head positioning.

The acuity of onset and presence or absence of pain can be used to prestratify diagnostic possibilities, as shown in Fig. 18.2, especially with regard to vascular, potentially ischemic events.

Symptoms

Monocular Cause. This is present only if the patient complains that the diplopia persists in the affected eye with the normal eye closed.

Mechanical Orbitopathy. A structural restriction of motion of a single eye, typically gradual in onset, may cause diplopia in a single or multiple directions of gaze, depending on the type and extent of muscular involvement. A sensation of mass effect, discomfort, or pain in the culprit eye is a characteristic symptom. If

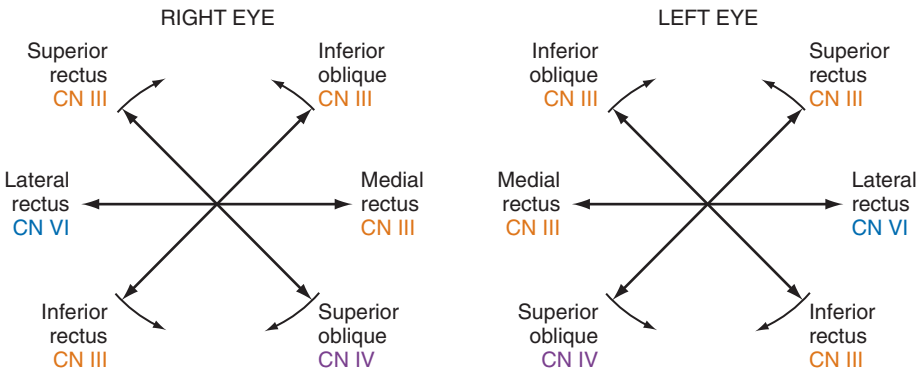


Fig. 18.1. Cardinal movements of the eyes, with the oculomotor muscles that create them and the nerves that supply those muscles. *Small curved arrows* denote intorsion or extorsion of the eye by the muscle indicated. *CN,* Cranial nerve.

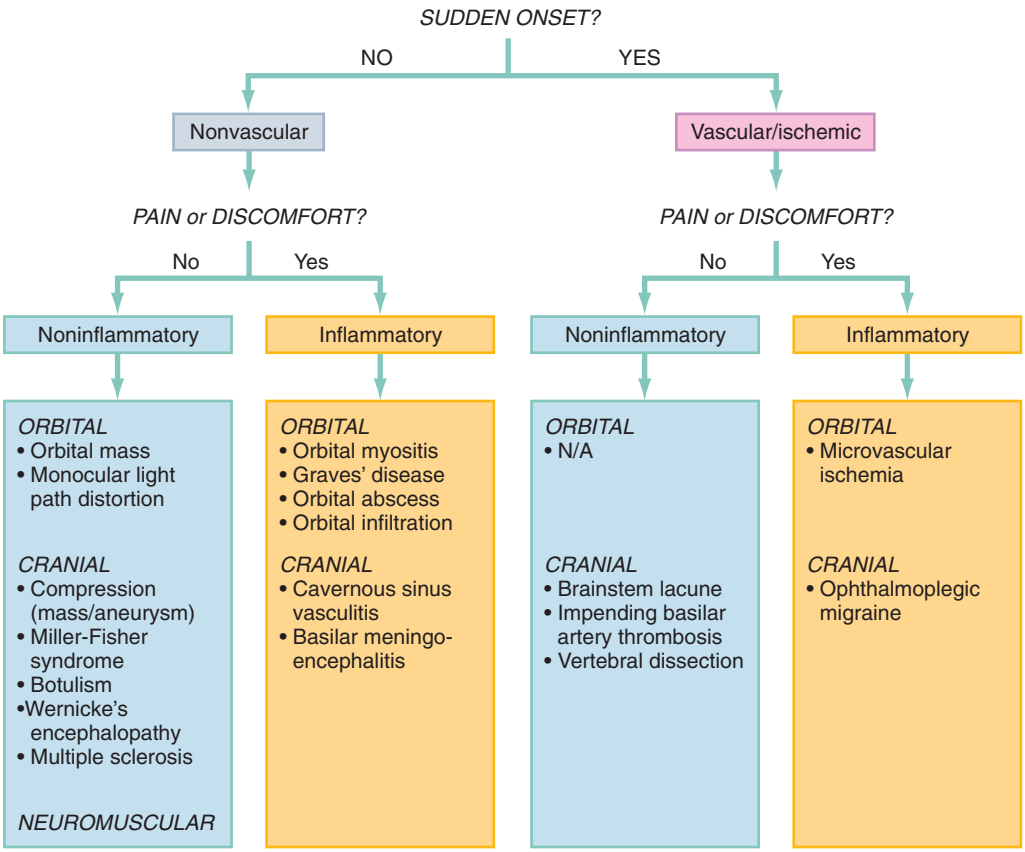


Fig. 18.2. Prestratification of the differential diagnosis in a patient presenting with diplopia.

the cause is infectious, the patient may have a history of a fever. Diplopia that is worse in the morning suggests Graves' myopathy, presumably due to the venous congestion of the ocular muscle associated with being supine.

Isolated Oculomotor Nerve Palsy. The patient with a CN III palsy typically reports diplopia in all directions of gaze, except on lateral gaze to the affected side. A CN IV palsy resulting in rotational double vision makes descending stairs, reading, and watching television in bed difficult. Diplopia that worsens on lateral gaze to one direction implies an issue with CN VI on that side.[2] A patient with diplopia from an isolated palsy of CN III, IV, or VI will typically not have other associated symptoms. Pain and speed of onset are differentiators; a sudden isolated CN III, CN IV, or CN VI palsy associated with orbital discomfort in a patient with chronic diabetes or hypertension strongly suggests that microvascular ischemia is the cause, with a caveat that with a CN III palsy, a headache frequently accompanies aneurysmal compression.[21]

The diplopia from a problem involving the cavernous sinus or orbital apex, unlike an isolated mononeuropathy, may manifest as a combination of any of the gaze abnormalities noted above, because more than one cranial nerve may be involved. It may be gradual in onset and associated with retroorbital pain or blurred vision due to venous congestion. Because branches of the trigeminal nerve travel though the orbital apex, the patient may have associated ipsilateral periorbital facial numbness or dysthesia.[7]

Neuroaxial Process Involving the Brainstem and Related Cranial Nerves. A focal brainstem lesion (eg, in multiple sclerosis) may result in isolated diplopia. However, localized brainstem lesions such as those from mass effect or ischemia typically also result in so-called neighborhood symptoms and signs from anatomically contiguous involvement, of which double vision may be the most prominent and therefore the presenting complaint (see Box 18.1). It is therefore important to screen for those other symptoms and signs actively. Additional symptoms of nausea, vertigo, or slurred speech are concerning for an impending basilar artery occlusion, especially if symptoms are sudden in onset, painless, and fluctuate, or a brainstem mass, if gradual in onset and progressive over days. A young person with an ophthalmoplegic migraine may present in a similar fashion to someone with a brainstem stroke but will typically develop an associated ipsilateral headache.

Diplopia from a more diffuse neurologic syndrome that happens to involve the brainstem and cranial nerves is usually gradual in onset and manifests with various other discordant symptoms. A gradually evolving combination of double vision, slurred speech, and problems swallowing suggests foodborne botulism,[16] especially if additional symptoms of dry mouth, nausea, and diffuse muscle weakness are present. Double vision, clumsiness, and altered mentation in a patient with chronic alcoholism, malnutrition, or history of bariatric surgery should raise the possibility of Wernicke's encephalopathy.[18] Diplopia and other cranial nerve symptoms, together with headache, photophobia, stiff neck, and/or fever, are suspicious for a basilar meningoencephalitis.

Neuromuscular Disorder. Diplopia that is variably triggered in multiple directions, and without a distinct structural or neuropathic cause evident, implies a neuromuscular cause such as myasthenia gravis. A mild neuromuscular manifestation of myasthenia may present with a diplopia isolated to one direction, however. Diplopia from neuromuscular disease generally fluctuates over time[2] and, in myasthenia gravis, worsens with fatigue and improves with rest.[22] There may be associated symptoms of proximal muscle weakness (eg, difficulty holding arms above the head or climbing stairs), shortness of breath, or difficulty swallowing.

Signs

Monocular Cause. With monocular diplopia—typically a problem with abnormal refraction—the diplopia from the affected eye should resolve when a pinhole is used, unless it is due to a retinal abnormality.

Mechanical Orbitopathy. Signs of a structural orbitopathy or myositis include proptosis, periorbital swelling, edema, conjunctival or scleral hyperemia, and palpebral swelling involving a single eye. Diplopia due to a mass in the orbit may appear as a clean, ordinal mechanical diplopia, in which having the patient attempt to look in the direction of the problem induces the most diplopia, with an axis of visual image separation parallel to the direction of the gaze (as can at times be seen in patients with significant periorbital swelling from trauma). In contrast, diplopia due to a process in any of the individual extraocular muscles, except for the lateral or medial recti muscles, may present in a messy eccentric or torsional manner based on the direction of pull of and therefore restriction by each muscle (see Fig. 18.1). There is a mismatch between the primary direction of diplopia and primary direction of movement, possibly improved by head tilt. Although findings may mimic a neurogenic palsy to some extent, the signs induced on testing extraocular eye movements will not reflect the stereotyped deficits typical of palsies of the oculomotor cranial nerves. Ocular myositis can be distinguished from a neurogenic palsy in that it abruptly restricts eye movement away from the muscle, whereas a cranial nerve palsy smoothly and progressively impairs movement toward the weakened muscle. Stigmata of Graves' disease include lid lag, diffuse conjunctival edema, and vascular injection[3] and, because it typically affects the inferior and medial recti muscles first, restriction of elevation and abduction of the eye. Patients with thyroid-related diplopia may tilt their head back to accommodate for the restriction of upward gaze by the thickened inferior rectus muscle.[2]

Isolated Oculomotor Nerve Palsy. Palsies from an isolated mononeuropathy of the oculomotor nerve will present with typical findings, as outlined in Fig. 18.3. CN III also innervates the levator palpebrae superioris muscle, which lifts the upper eyelid, and provides parasympathetic innervation to two intrinsic ocular muscles, the ciliary and constrictor pupillae muscles, which

BOX 18.1

Lacunar Stroke Syndromes Presenting With Diplopia

Weber syndrome (midbrain lacune)—ipsilateral CN III palsy and contralateral hemiparesis
Benedikt syndrome (midbrain lacune)—ipsilateral CN III palsy and contralateral tremor or dysmetria
Claude syndrome (midbrain lacune)—ipsilateral CN III palsy and contralateral weakness, tremor, and ataxia
Millard-Gubler syndrome (pontine lacune)—ipsilateral CN VI palsy, ipsilateral facial weakness (CN VII), contralateral arm and leg weakness
Foville's syndrome (pontine tegmentum)—ipsilateral CN VI palsy, ipsilateral facial weakness (CN VII), contralateral ataxia and hemiparesis
One-and-a-half syndrome (CN VI nuclei, paramedian pontine reticular formation)—bilateral CN VI (abduction) palsies with a unilateral adduction palsy

Adapted from Friedman DI. Pearls: diplopia. Semin Neurol 30:54–65, 2010; and Lewandowski CA, Rao CP, Silver B: Transient ischemic attack: definitions and clinical presentations. Ann Emerg Med 52:S7–S16, 2008.

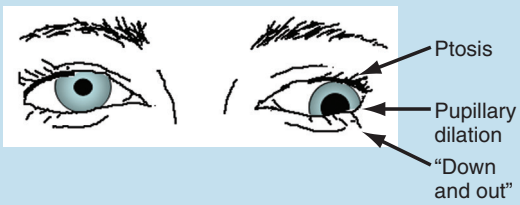
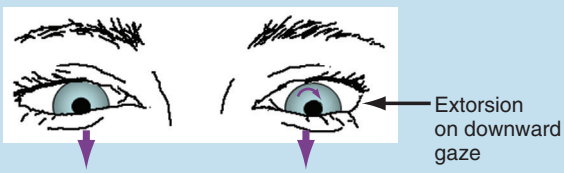
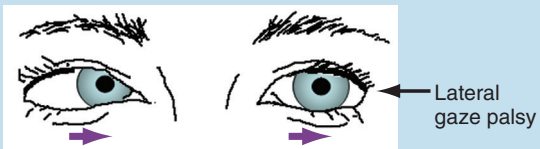
NERVE PALSY	MUSCLE(S) "OFF"	SYMPTOMS	EXAMINATION FINDINGS
Normal	N/A	N/A	
Oculomotor (CN III)	Medial, inferior, and superior rectii muscles • Inferior oblique muscle • Levator palpebrae (eyelid) • Ciliary and constrictor pupillae muscles (pupil)	Multidirectional horizontal and vertical diplopia, except on lateral gaze to the affected side • Eyelid "droop"	
Trochlear (CN IV)	Superior oblique muscle	Rotational diplopia that worsens on looking down and toward the nose	
Abducens (CN VI)	Lateral rectus muscle	Horizontal diplopia on gaze toward the affected side	

Fig. 18.3. Corresponding muscle dysfunction, symptoms and examination findings for each oculomotor cranial nerve palsy. *CN,* Cranial nerve.

constrict the pupil. An isolated CN III palsy presents with diplopia in all directions of gaze, except on lateral gaze to the affected side and an eye that is deviated down and out, with a dilated pupil, and ptosis. Typically seen in older patients with vascular risk factors such as diabetes and hypertension, diplopia due to microvascular ischemia may present with an isolated CN III palsy associated with pain, classically sparing the pupil, whereas that from compression (ie, from an aneurysm) is associated with pupillary mydriasis due to compression of pupillomotor parasympathetic fibers in the exterior of the nerve. The so-called rule of the pupil—more of a guideline than a rule—states that an otherwise complete CN III palsy (complete ptosis, completely down and out), with normal pupillary size and reactivity, rules out compression as the source. However, the presence of pupillary involvement does not rule in mechanical compression as the cause. A large case series of patients with CN III palsies revealed that over 50% of patients with diabetic microvascular ischemia had pupillary involvement, possibly from concomitant autonomic neuropathy, although pain was more common with CN III palsies from aneurysms (94% of cases) than from diabetic microvascular ischemia (69% of cases).[21] A rotational diplopia that worsens on looking down and toward the nose implies a superior oblique (CN IV) palsy. An abducens nerve (CN VI) palsy may present with bilateral findings, because elevated intracranial pressure from a brain tumor or malfunction ventriculoperitoneal shunt may be the cause.[23]

In contrast to a mononeuropathy, the combination of ipsilateral palsies of CN III, IV, and VI from an orbital apex or cavernous sinus process will typically present with additional findings—together called orbital apex syndrome—of exophthalmos, chemosis, and injection. Sensory deficits corresponding to the ophthalmic (V1) and maxillary (V2) divisions of the trigeminal nerve may be present, given their course through the orbital apex.

Neuroaxial Process Involving the Brainstem and Related Cranial Nerves. Vertical diplopia without the torsional component seen with CN IV palsy, called a vertical skew deviation, suggests a brainstem lesion. An internuclear ophthalmoplegia, suggested by an inability to adduct the eye on one side in the contralateral direction during lateral gaze that resolves during convergence, implicates a lesion in the medial longitudinal fasciculus (MLF) such as that typically found in patients with multiple sclerosis.[2] In multiple sclerosis, diplopia may present alone as a clinically isolated syndrome[4] or may be associated with a host of additional heterogeneous neurologic findings that typify this disorder (eg, optic neuritis, with blurred vision and eye pain, or focal motor or sensory abnormalities). A brainstem lacunar stroke may present as any of a number of identifiable syndromes (see Box 18.1). An impending basilar occlusion may present with additional symptoms of nystagmus, dysmetria, gait ataxia, and dysarthria.

A brainstem or cranial neuropathy that is part of a more diffuse neurologic syndrome may present with a stereotypical assortment of additional associated deficits. With foodborne botulism, patients have a descending flaccid paralysis that begins with multiple cranial nerve palsies. There may also be autonomic signs such as dry mouth, ileus, postural hypotension, respiratory muscle weakness, and pupillary abnormalities.[16] Patients with Miller-Fisher syndrome may present with an isolated ophthalmoplegia, considered a forme fruste of the disease, but more typically have the classic triad of ophthalmoplegia, ataxia, and areflexia. Muscle weakness should not be present[17]; if it is, the case is better classified as Guillain-Barré syndrome with

ophthalmoplegia.[17] Most patients with Wernicke's encephalopathy have ocular abnormalities, including nystagmus and ophthalmoplegia (usually from a CN VI palsy), typically associated with the classic triad of nystagmus, altered mental status, and ataxia. A fever suggests the possibility of an infectious process such as basilar meningoencephalitis.

Neuromuscular Disorder. The stigmata of neuromuscular disease such as muscle atrophy or weakness may be apparent on physical examination. Patients with myasthenia gravis may have unilateral or bilateral ptosis, weakness on forced eyelid closure, and generalized muscle weakness, but with normal reflexes and no sensory abnormalities. About 50% present with isolated ocular abnormalities.[22] The diplopia may represent a myasthenic crisis, possibly associated with occult respiratory muscle weakness and ventilatory insufficiency.[24]

Ancillary Testing

The patient with monocular diplopia should undergo a slit lamp and funduscopic examination and may need an evaluation by an ophthalmologist. A monocular cause of diplopia will not typically require an extensive neuroophthalmologic evaluation.

In the patient with a suspected or evident mechanical orbitopathy, a magnetic resonance imaging (MRI) scan of the orbits with gadolinium can allow an assessment for enlargement or enhancement in extraocular muscles and orbital structures, although a contrast-enhanced cranial computed tomography (CT) scan with fine cuts through the orbit can be used as a second-line option.[25] The same imaging paradigm applies to localization of the process within the cavernous sinus or orbital apex, because it will highlight infiltrative, inflammatory, or compressive pathology.[25]

For an isolated neuropathy of CN III, IV, or VI presenting without evidence of an aneurysm, the optimal study is MRI of the brain and orbits with gadolinium, high-resolution cuts through the brainstem, and fat-suppressed orbital imaging to assess for inflammation, neoplasm, or demyelination along the course of the nerves.[25] If an aneurysm is suspected, the imaging modality chosen (typically magnetic resonance angiography [MRA] and CT angiography) should be standard for that required to assess for an aneurysm; this is detailed in other chapters in this text specifically devoted to the topic.

If myasthenia gravis is suspected, a bedside test that can be performed is the ice test. An ice-filled glove or bag is applied to the patient's closed eye or eyes, held there for about 5 minutes, withdrawn, and any improvement in ptosis (typically ≈5 mm) or diplopia noted. Cold temperatures mitigate the effect of myasthenia-related acetylcholine receptor blockade by decreasing cholinesterase activity and promoting the efficacy of acetylcholine at the endplate. The bedside tests with the highest sensitivities for ocular myasthenia gravis are fatigability on sustained upgaze (sensitivity, 80%; specificity, 63%) and the ice test (sensitivity, 80%; specificity, 25%).[22] An edrophonium (Tensilon) challenge can also be performed, if the drug is available.

DIAGNOSTIC ALGORITHM

The critical, emergent, and urgent diagnoses applicable to each of the differential considerations noted are outlined in Table 18.1. The refinement of the differential diagnosis for the ED patient with diplopia involves determining the exact nature of the diplopia and functional location of the defect and screening for associated symptoms and findings that may suggest the underlying cause. Most of this diagnostic resolution is done at the bedside, followed by targeted neuroophthalmologic imaging, as indicated. The diagnostic challenge, in a context of cost-effective and efficient resource utilization, tends to be "Where do I look? … and for what? … and with which tool?" This challenge can be addressed, as reflected in the diagnostic algorithm in Fig. 18.4, using a phased systematic approach that incorporates the following queries, taking into consideration the symptoms and signs described earlier (see "Pivotal Findings"):

1. Is the diplopia monocular?
2. Is the diplopia due to a restrictive, mechanical orbitopathy?
3. Is the diplopia due to a palsy of the oculomotor cranial nerves (CN III, IV, VI) in a single eye?
4. Is the diplopia due to a neuroaxial process involving the brainstem and related cranial nerves?
5. Is the diplopia due to a neuromuscular disorder?

The first key assessment is to determine if diplopia is purely monocular. If it is, the evaluation essentially ends with ophthalmologic considerations. In contrast, if the diplopia is determined to be binocular, the next question is whether or not there is a simple mechanical orbitopathy, from an inflammatory, traumatic, neoplastic, or infectious mass effect directly restricting the movement of a single eye. If both eyes are involved, thyroid disease (Graves' orbitopathy) is a consideration. If an orbital mechanical problem is clearly apparent, with no neuroophthalmologic findings (including ptosis, pupillary abnormality, and anisocoria) or neurologic findings (including cranial nerve abnormalities), the initial evaluation can proceed along these lines.

If the diplopia does not appear to be strictly mechanical, the next question is whether there is a unilateral oculomotor cranial nerve palsy in the oculomotor (CN III), trochlear (CN IV), or abducens (CN VI) nerve, either as an isolated simple mononeuropathy from compression or microvascular ischemia or ipsilateral involvement of more than one of these oculomotor nerves (from mass, inflammation, or infection in the posterior orbit or cavernous sinus; orbital apex syndrome). An older diabetic patient with a classic presentation of mononeuropathy from microvascular ischemia will typically not need neuroimaging because the yield regarding another pathology is very low.[6,26] If there is any equivocation, however, it would not be unreasonable to pursue this in the ED because a small percentage of patients with risk factors for microvascular ischemia (eg, hypertension, diabetes, smoking) may have a cause other than microvascular ischemia.[6,27]

Assuming that a unilateral process limited exclusively to the orbit or oculomotor cranial nerves is not clearly identifiable, the next option is a neuroaxial process involving the brainstem and related cranial nerves, as one of the following: (1) a focal lesion in the brainstem (eg, from multiple sclerosis); (2) a more diffuse but still localized brainstem process (eg, from a brainstem tumor, brainstem lacunar stroke, impending basilar artery thrombosis, vertebral artery dissection, or ophthalmoplegic migraine); or (3) as part of a more diffuse neurologic syndrome involving the brainstem and/or CNs III, IV, and VI due an infectious, autoimmune, neurotoxic, or metabolic process involving other neurologic structures (eg, basilar meningoencephalitis, foodborne botulism, Miller-Fisher or Guillain-Barré syndrome, Wernicke's encephalopathy). It should be kept in mind that diplopia may be the first, primary, or only symptom of any of these, and that neuropathic signs suggesting a focal brainstem process may actually be a mild or early presentation of a diffuse neurologic syndrome.

Finally, if the presentation of the diplopia does not fit into an anatomically congruent process or central nervous system (CNS), a neuromuscular cause such as myasthenia gravis or tick paralysis may be involved.

EMPIRICAL MANAGEMENT

Because the treatment of diplopia depends entirely on the cause, there are few primary treatments for diplopia in the ED, as opposed to addressing whatever secondary disorder is causing it. Such approaches are outlined elsewhere in this text.

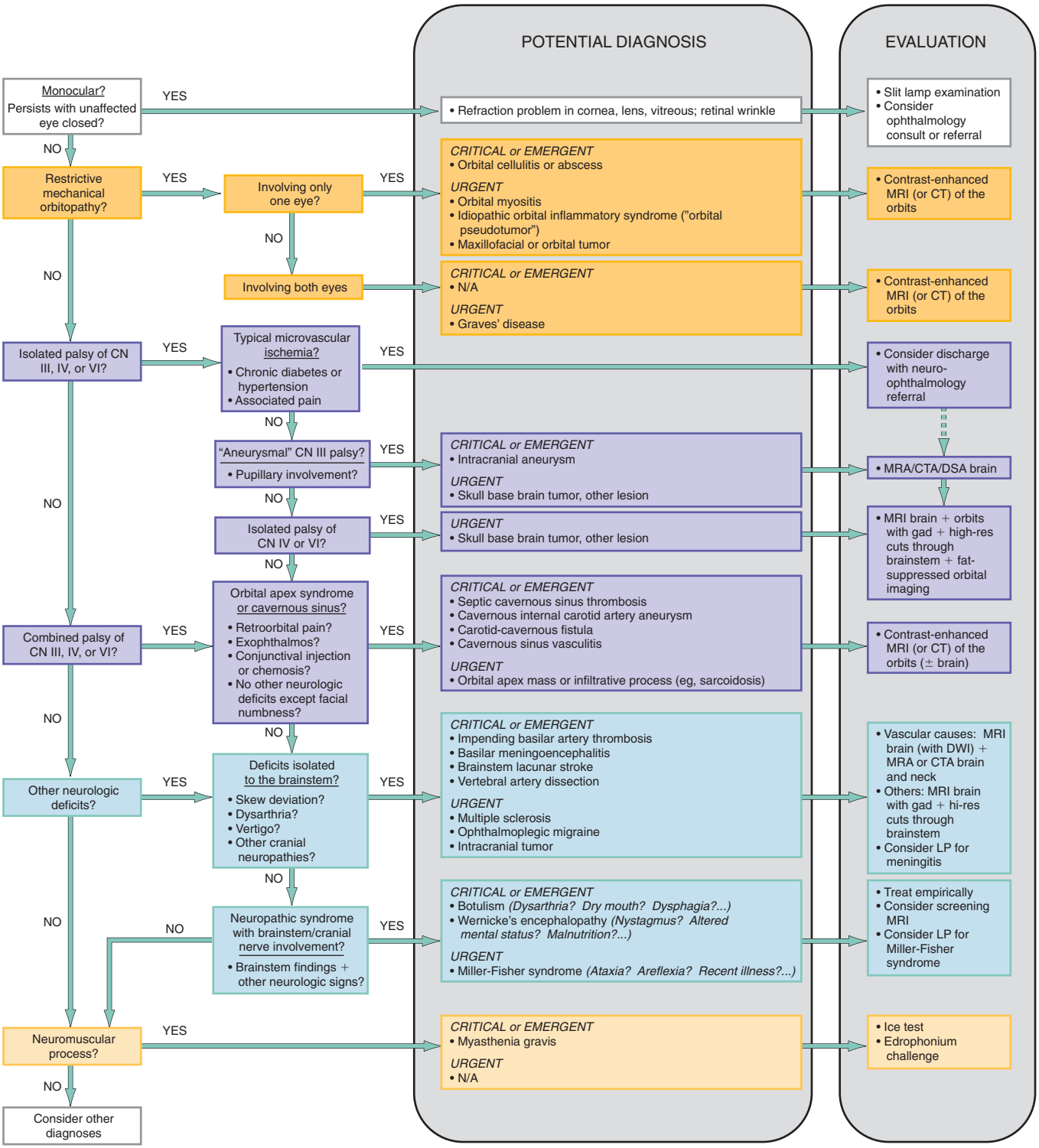


Fig. 18.4. Algorithm for the diagnostic approach to diplopia in the ED, a guideline. *CN,* Cranial nerve; *CNS,* central nervous system; *CT,* computed tomography; *CTA,* CT angiography; *DSA,* digital subtraction angiography (conventional angiography); *DWI,* diffusion-weighted imaging; *gad,* gadolinium; *High-res,* high-resolution; *LP,* lumbar puncture; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging.

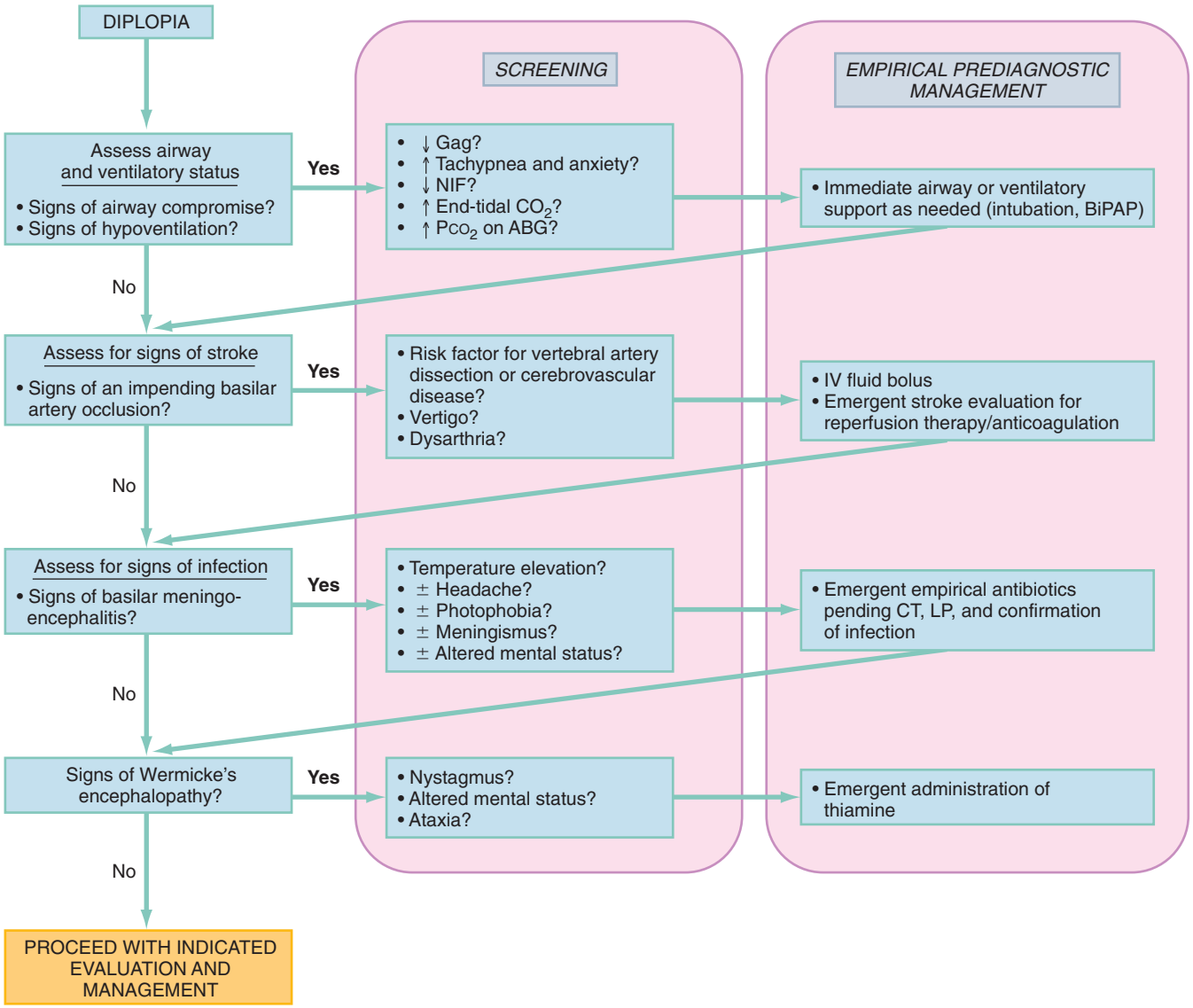


Fig. 18.5. Algorithm for the initial stabilization of the patient with diplopia in the ED, a guideline. *ABG,* Arterial blood gas; *BiPAP,* biphasic positive airway pressure; *CO_2,* carbon dioxide; *pCO_2,* partial pressure of carbon dioxide; *CT,* computed tomography (of the cranium); *LP,* lumbar puncture; *NIF,* negative inspiratory force.

Management Algorithm

Certain emergent therapeutic measures may be indicated in the context of potentially serious underlying causes, as outlined in the algorithm in Fig. 18.5. The priority is to consider imminent threats to CNS tissue viability such as an impending basilar artery thrombosis and then consider rapidly evolving threats to CNS tissue viability such as meningoencephalitis or Wernicke's encephalopathy and institute indicated treatments empirically as, or even before, the evaluation gets underway.

The patient with diplopia will typically require admission for further evaluation and treatment of the underlying disorder, unless diagnosed with a low-acuity condition such as microvascular ischemia. A CN III or VI palsy from microvascular ischemia is generally self-limited; the pain usually resolves after a few days, and complete spontaneous resolution is the norm, occurring in up to 95% of patients. These patients can typically be discharged home, with close outpatient follow-up.

KEY CONCEPTS

- Monocular diplopia persists in one affected eye, even with the other one closed. It is an ophthalmologic problem related to refractory distortions in the light path or from buckling of the retina.
- Binocular diplopia resolves when either eye is closed and is the result of a misalignment in the visual axes.
- Four lines of questioning that help formulate the differential diagnosis of binocular diplopia are as follows: (1) cadence of onset and symptoms (a sudden onset suggests an ischemic event; a fluctuation of symptoms suggests transient ischemic attacks, impending stroke, or neuromuscular disease); (2) directionality and orientation of the diplopia (horizontal, vertical, torsional); (3) presence of pain, which suggests an inflammatory or infectious process, and (4) the presence of other associated symptoms, which suggest a larger disease process (eg, infection, CNS ischemia, neuromuscular disease).
- The diagnostic approach to diplopia entails a methodical consideration of (1) a monocular (refractive) problem, which, when excluded, leads to consideration of (2) a simple restrictive, mechanical orbitopathy, which, when excluded, leads to consideration of (3) a palsy of one or more of the oculomotor cranial nerves, and then (4) a more proximal neuroaxial process involving the brainstem and related cranial nerves; if all else is excluded, then (5) a systemic neuromuscular process.
- An isolated CN III palsy presents with diplopia in all directions of gaze, except on lateral gaze to the affected side, and an eye that is deviated down and out, with a dilated pupil, and ptosis. Microvascular ischemia (typically seen in patients with diabetes), classically spares the pupil. A CN IV palsy results in rotational diplopia that worsens on looking down and toward the nose. A CN VI palsy results in diplopia that worsens on lateral gaze toward the problematic side.
- Simultaneous ipsilateral involvement of more than one of the CN III, IV, or VI nerves from mass, inflammation, or infection in the posterior orbit or cavernous sinus (orbital apex syndrome) may cause a combination of palsies and is associated with retroorbital pain or blurred vision due to venous congestion and possibly ipsilateral numbness or dysesthesia from involvement of the ophthalmic (V1) and maxillary (V2) trigeminal branches that travel though the orbital apex.
- Diplopia from a neuroaxial process involving the brainstem and related cranial nerves may present as (1) a focal lesion in the brainstem (eg, from multiple sclerosis), (2) a more diffuse but still localized brainstem process (eg, from a brainstem tumor or lacunar stroke, impending basilar artery thrombosis, vertebral artery dissection, or an ophthalmoplegic migraine), or (3) as part of a more diffuse neurologic syndrome involving the brainstem and oculomotor nerves (eg, from an infectious, autoimmune, neurotoxic, or metabolic process).
- The diplopia in myasthenia gravis is associated with ptosis, gets worse as the patient fatigues, and improves with rest or on placing ice over the eye.
- The empirical treatment of conditions causing diplopia, instituted even before testing for specific entities is begun, is directed toward imminent threats to airway and ventilation (eg, with botulism and myasthenia gravis), immediate threats to CNS tissue viability (eg, with basilar artery thrombosis or stroke), and rapidly evolving threats to CNS tissue viability (eg, with meningoencephalitis or Wernicke's encephalopathy).

The references for this chapter can be found online by accessing the accompanying Expert Consult website.

REFERENCES

1. Nazerian P, Vanni S, Tarocchi C, et al: Causes of diplopia in the emergency department: diagnostic accuracy of clinical assessment and of head computed tomography. Eur J Emerg Med 21:118–124, 2014.
2. Friedman DI: Pearls: diplopia. Semin Neurol 30:54–65, 2010.
3. Cockerham KP, Chan SS: Thyroid eye disease. Neurol Clin 28:729–755, 2010.
4. Prasad S, Volpe NJ: Paralytic strabismus: third, fourth, and sixth nerve palsy. Neurol Clin 28:803–833, 2010.
5. Cianfoni A, Pravatà E, De Blasi R, et al: Clinical presentation of cerebral aneurysms. Eur J Radiol 82:1618–1622, 2013.
6. Tamhankar MA, Biousse V, Ying GS, et al: Isolated third, fourth, and sixth cranial nerve palsies from presumed microvascular versus other causes: a prospective study. Ophthalmology 120:2264–2269, 2013.
7. Aryasit O, Preechawai P, Aui-Aree N: Clinical presentation, aetiology and prognosis of orbital apex syndrome. Orbit 32:91–94, 2013.
8. Boynes SG, Echeverria Z, Abdulwahab M: Ocular complications associated with local anesthesia administration in dentistry. Dent Clin North Am 54:677–686, 2010.
9. Kurimoto T, Tonari M, Ishizaki N, et al: Orbital apex syndrome associated with herpes zoster ophthalmicus. Clin Ophthalmol 5:1603–1608, 2011.
10. Lee CY, Tsai HC, Lee SS, et al: Orbital apex syndrome: an unusual complication of herpes zoster ophthalmicus. BMC Infect Dis 15:33, 2015.
11. Merino-Iglesias A, Montero JA, Calabuig-Goena M, et al: Orbital apex syndrome secondary to herpes zoster virus infection. BMJ Case Rep 2014:2014.
12. Mattle HP, Arnold M, Lindsberg PJ, et al: Basilar artery occlusion. Lancet Neurol 10:1002–1014, 2011.
13. Muslikhan Y, Hitam WH, Ishak SR, et al: Cryptococcus meningitis in an immunocompetent teenage boy presented early with diplopia. Int J Ophthalmol 3:92–94, 2010.
14. Jensen MB: Diplopia secondary to West Nile virus meningitis. Webmedcentral 1:2010.
15. Rufa A, Cerase A, Annunziata P, et al: Transient supranuclear paresis of the abduction in viral encephalitis of the brainstem. Neurol Sci 31:653–655, 2010.
16. Williams BT, Schlein SM, Caravati EM, et al: Emergency department identification and critical care management of a Utah prison botulism outbreak. Ann Emerg Med 64:26–31, 2014.
17. Arányi Z, Kovács T, Sipos I, et al: Miller Fisher syndrome: brief overview and update with a focus on electrophysiological findings. Eur J Neurol 19:15–20, 2012.
18. Lough ME: Wernicke's encephalopathy: expanding the diagnostic toolbox. Neuropsychol Rev 22:181–194, 2012.
19. Lonati D, Giampreti A, Rossetto O, et al: Neurotoxicity of European viperids in Italy: Pavia Poison Control Centre case series 2001-2011. Clin Toxicol (Phila) 52:269–276, 2014.
20. Spillane J, Higham E, Kullmann DM: Myasthenia gravis. BMJ 345:e8497, 2012.
21. Keane JR: Third nerve palsy: analysis of 1400 personally-examined inpatients. Can J Neurol Sci 37:662–670, 2010.
22. Mittal MK, Barohn RJ, Pasnoor M, et al: Ocular myasthenia gravis in an academic neuro-ophthalmology clinic: clinical features and therapeutic response. J Clin Neuromuscul Dis 13:46–52, 2011.
23. Teksam O, Keser AG, Konuskan B, et al: Acute abducens nerve paralysis in the pediatric emergency department: analysis of 14 patients. Pediatr Emerg Care 32:307–311, 2016.
24. Wendell LC, Levine JM: Myasthenic crisis. Neurohospitalist 1:16–22, 2011.
25. Wippold FJ, II, Cornelius RS, Berger KL, et al: Expert Panel on Neurologic Imaging: Orbits, vision and visual loss. <www.ajnr.org/content/31/1/196.full>.
26. Murchison AP, Gilbert ME, Savino PJ: Neuroimaging and acute ocular motor mononeuropathies: a prospective study. Arch Ophthalmol 129:301–305, 2011.
27. O'Colmain U, Gilmour C, MacEwen CJ: Acute-onset diplopia. Acta Ophthalmol 92:382–386, 2014.
28. Lewandowski CA, Rao CP, Silver B: Transient ischemic attack: definitions and clinical presentations. Ann Emerg Med 52:S7–S16, 2008.

CHAPTER 18: QUESTIONS & ANSWERS

18.1. A 65-year-old man with a long-standing history of diabetes and hypertension presents with sudden onset of persistent diplopia that began a few hours before arrival. He describes left retro-orbital discomfort, and his examination is notable for a left eye that is deviated laterally and downward, with a palsy of movement medially and upward. He also has a left-sided ptosis but no conjunctival injection, chemosis, or proptosis. His pupils are equal in size at 4 mm, round, and equally reactive to light in both a direct and consensual reflex, and his examination is otherwise unremarkable. What is the most likely cause of the diplopia?

A. Brain tumor
B. Cerebral aneurysm
C. Microvascular ischemia
D. None of these
E. Orbital apex syndrome

Answer: C. Based on examination, this is a patient who has a pupil-sparing CN III (third nerve) palsy. Because his pupillary examination is normal, with an otherwise complete CN III palsy, the so-called rule of the pupil applies. The palsy is very unlikely to be due to external compression from a brain tumor, aneurysm, or orbital apex process. It is a typical presentation of microvascular ischemia, to which the patient is predisposed, given his history of diabetes and hypertension.

18.2. A 56-year-old woman presents with recurrent episodes of diplopia that have been ongoing for a week. She describes double vision that gradually comes and goes, typically worse at the end of the day, with no particular direction or orientation to the diplopia. The patient's coworker, who is present in the emergency department (ED) with her, states that the patient's eyes "looked droopy" during an animated staff meeting they attended that afternoon but look normal now. The patient also describes waxing and waning general muscular weakness that has also been present this past week but denies any other symptoms and states that when she rests, she feels better. With which entity are her symptoms most consistent?

A. Botulism
B. Hypothyroidism
C. Miller-Fisher syndrome
D. Myasthenia gravis
E. None of the above

Answer: D. The patient and coworker are describing what appears to be an activity-related diplopia, with generalized muscle weakness and lack of other focal symptoms, all very suggestive of a possible neuromuscular process (myasthenia gravis). Miller-Fisher syndrome would not be associated with muscle weakness and would not wax and wane. Botulism would typically have a more progressive course, with other associated bulbar symptoms. Diplopia may be associated with hypothyroidism if it is a presentation of or treatment complication of Graves' disease but would not change so markedly with activity.

18.3. A 76-year-old man with hypertension, hypercholesterolemia, and diet-controlled diabetes presents with a sudden onset of diplopia that developed 30 minutes before arrival. Medics state that the patient's wife reported that he suddenly began staggering around the room, unable to bear weight on his left side. On examination, the patient has normal vital signs except for mild hypertension and has a right CN III palsy, with left arm and leg weakness. He has no airway complaints and denies any pain. What is the most appropriate initial response?

A. Checking blood gas levels and assess the patient's negative inspiratory force
B. Emergent treatment with botulinum antitoxin
C. Initiating broad-spectrum antibiotics to cover upper respiratory pathogens
D. Initiating clinical measures to address an acute ischemic stroke
E. A and B

Answer: D. The paroxysmal onset of the patient's symptoms, with focal neurologic symptoms and signs, suggests an ischemic event. His crossed deficits and discrete CN III palsy suggest localization in the brainstem.

18.4. Which constellation of symptoms is most concerning for foodborne botulism?

A. Double vision, headache, and right leg weakness
B. Double vision, left eye discomfort, and periorbital swelling
C. Double vision, neck pain, and vertigo
D. Double vision, nystagmus, and confusion
E. Double vision, slurred speech, difficulty swallowing, and dry mouth

Answer: E. Double vision, slurred speech, difficulty swallowing, and dry mouth would be present with foodborne botulism.

18.5. A 45-year-old man presents with progressively worsening double vision associated with right-sided, retro-orbital pain. His examination reveals mild conjunctival injection of the right eye, palsies of CNs III, IV, and VI on that side, some ptosis, a slightly decreased visual acuity to the right eye compared to the left, and mild sensory loss to the right infraorbital maxillary area. Which of the following initial imaging modalities should be used to evaluate the patient?

A. Computed tomography angiography (CTA) or magnetic resonance angiography (MRA) of the brain and neck
B. Contrast-enhanced CT or magnetic resonance imaging (MRI) of the brain, with fine cuts through the orbit
C. Diffusion-weighted MRI of the brain and brainstem
D. Digital subtraction angiography (DSA)
E. Noncontrast computed tomography of the brain

Answer: B. The combined palsy of multiple oculomotor cranial nerves on one side, with no other neurologic deficits apart from mild facial numbness corresponding to the maxillary branch of the trigeminal nerve, especially with the ocular findings and decreased visual acuity, suggests an orbital apex or cavernous sinus problem. The most optimal study would be that outlined in answer B. The risk in using the studies outlined in the other answers is that pathology might be missed because they are not dedicated to the orbits and cavernous sinus.