Diagnosis and Management of Ophthalmic Emergencies in the Hospital

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KEYWORDS

• Papilledema • Optic disc edema • Sudden vision loss • Third cranial nerve palsy • Third nerve palsy • Endophthalmitis • Endogenous endophthalmitis

HOSPITAL MEDICINE CLINICS CHECKLIST

1. Papilledema is defined as bilateral optic disc swelling caused by increased intracranial pressure.
2. Papilledema is most commonly caused by intracranial mass lesions, idiopathic intracranial hypertension, hydrocephalus, intracranial hemorrhage, venous thrombosis or obstruction, meningitis, and cerebral edema.
3. Emergent neuroimaging of the brain is critical in diagnosis of the patient with papilledema.
4. Vision loss caused by giant cell arteritis should be treated immediately with corticosteroids to prevent involvement of the second eye.
5. In complete third cranial nerve palsy with pupil involvement, the affected eye is turned out and slightly down, with a paralysis of adduction, elevation, and depression, ptosis, and a dilated unreactive pupil.
6. Third nerve palsy may be an early sign of a neurologic emergency, such as an intracranial aneurysm, pituitary apoplexy, uncal herniation, or giant cell arteritis.
7. In third nerve palsy, computed tomography (CT) and CT angiography should be performed emergently to rule out aneurysm.

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8. If these imaging studies are negative according to review by an experienced radiologist, then magnetic resonance imaging should be performed if the patient is at low risk for a microvascular ischemic cause.
9. Endogenous endophthalmitis is a rare disease, with potentially devastating consequences. Early recognition and treatment are essential to improve the chances of preserving vision.

PAPILLEDEMA

Definitions

How is papilledema defined?

Papilledema is defined as bilateral optic disc swelling caused by increased intracranial pressure (ICP).

Differential Diagnosis

What is the differential diagnosis of optic disc swelling?

Causes of optic nerve swelling are listed in **Box 1**.

Optic disc swelling can be mimicked by congenitally anomalous, elevated optic discs. Unlike optic disc swelling, congenitally anomalous discs do not usually show disc margin blurring, hemorrhages, or cotton-wool spots. They usually do not cause vision loss and do not show leakage of intravenously injected fluorescein dye.

Epidemiology

What are the most common causes of papilledema?

Box 2 lists the causes of papilledema, grouped by frequency.

Can medications cause papilledema?

Yes, tetracycline, minocycline, vitamin A derivatives (isotretinoin), growth hormone, and steroid withdrawal can cause papilledema.

History and Examination

Which symptoms are associated with papilledema?

- Headaches (may be positional and worsen with Valsalva maneuvers)
- Nausea and vomiting
- Pulsatile tinnitus
- Transient visual obscurations (often bilateral, lasting for seconds, and may be precipitated by changes in position)
- Diplopia (most commonly from sixth nerve palsy, and may be unilateral or bilateral)

Box 1
Causes of optic disc swelling

Increased ICP (papilledema)
Inflammatory
- Infectious
- Demyelinating disease
- Sarcoidosis

Metabolic
- Diabetic papillopathy

Ischemic
- Anterior ischemic optic neuropathy
  - Arteritic (giant cell arteritis)
  - Nonarteritic
- Central retinal vein occlusion

Malignant hypertension
Compressive
- Neoplastic: meningioma, hemangioma, or other orbital tumors
- Nonneoplastic: thyroid eye disease

Infiltrative
- Neoplastic: leukemia, lymphoma, glioma, plasma cell dyscrasias
- Nonneoplastic: sarcoidosis

Hereditary: Leber optic neuropathy
Ocular hypotony

Box 2
Causes of papilledema

Common	Uncommon
Intracranial mass lesion	Dural sinus arteriovenous malformation
Idiopathic intracranial hypertension (pseudotumor cerebri)	Guillain-Barré syndrome
Hydrocephalus	Chronic inflammatory demyelinating polyneuropathy
Intracranial hemorrhage	Spinal cord tumors
Venous thrombosis/obstruction	Craniosynostoses
Meningitis	Nonaccidental injury
Cerebral edema	

Adapted from Liu GT, Volpe NJ, Galetta SL. Optic disc swelling: papilledema and other causes. In: Neuro-ophthalmology: diagnosis and management. 2nd edition. Philadelphia: WB Saunders; 2010. p. 199–236.

What are the key examination findings?

- Optic disc swelling
- Sometimes visual field defects
- Visual acuity is often normal

In acute papilledema, optic disc swelling is accompanied by hyperemia and blurring of the disc margins (**Fig. 1**), often obscuring the underlying vessels. Retinal hemorrhages, cotton-wool spots (infarcts), and dilated, tortuous retinal veins may also develop. The optic disc swelling is usually bilateral but may be asymmetric.

The development of papilledema lags behind ICP increase and usually requires 1 to 5 days of persistent increase of ICP. However, sudden increases in ICP, such as with intracranial hemorrhage, may occasionally cause papilledema within hours.[1]

Diagnosis

Which clinical features help guide the differential diagnosis for papilledema?

A thorough history and examination, including blood pressure measurement, are critical in evaluating a patient with papilledema. Seizures and focal neurologic deficits are suggestive of a mass lesion. Fever, headache, stiff neck, and altered mental status suggest meningitis. Sudden onset of a severe headache, altered mental status, and neurologic deficits suggest an acute intracranial hemorrhage. A young, overweight female with recent weight gain or history of tetracycline (or derivatives) use is suggestive of idiopathic intracranial hypertension.

Which tests are used for evaluation of papilledema?

Emergent neuroimaging of the brain is essential in diagnosis of the patient with papilledema. Magnetic resonance imaging (MRI) with gadolinium is preferred to assess for mass lesions, hemorrhage, or hydrocephalus. Computed tomography (CT) with contrast may be used if MRI is not available. Magnetic resonance venography or CT venography should be performed if venous thrombosis or obstruction is suspected. If neuroimaging is normal, then lumbar puncture with cerebrospinal fluid (CSF) analysis and opening pressure measurement is necessary to rule out meningitis and to assess for idiopathic intracranial hypertension.[2]

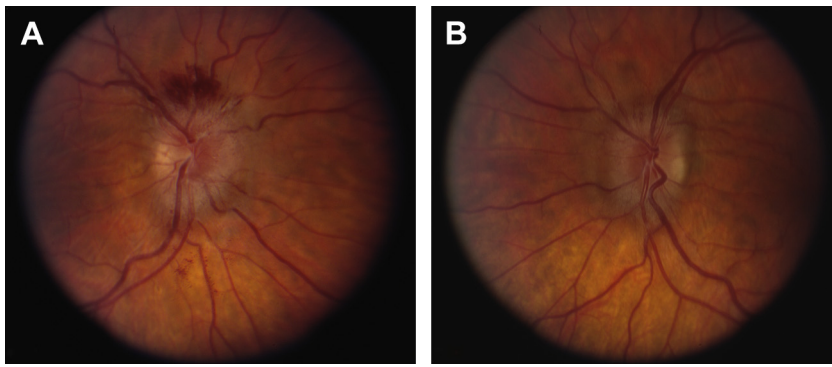

Fig. 1. Papilledema with bilateral optic disc elevation, hyperemia, blurring of the optic disc margins, and hemorrhages of the superior right optic disc.

Management

Which patients should be hospitalized?

The need for hospitalization is dependent on the underlying cause and the severity of the increased ICP. Patients with intracranial hemorrhage, venous thrombosis, meningitis, and intracranial mass lesions may require hospitalization. Idiopathic intracranial hypertension generally does not require hospitalization.

Which patients require inpatient ophthalmology consultation?

Inpatient ophthalmology or neuro-ophthalmology consultation should be obtained if the underlying cause of the papilledema has not been established. Outpatient ophthalmology follow-up is also helpful for serial visual acuity and visual field testing to monitor for progression or improvement.

How should patients be managed long-term?

Management is directed at the underlying cause of the papilledema.

- Intracranial mass lesions require neurosurgical consultation.
- Idiopathic intracranial hypertension treatment depends on the severity of vision loss and other symptoms. Patients without vision loss, headache, and other symptoms may be managed with modest weight reduction (5%–10% of total body weight), a low salt diet, analgesics or tricyclic antidepressants, and close observation. In patients with mild vision loss, acetazolamide, furosemide, or topiramate may be added. Patients who fail medical therapy or have severe or progressive vision loss may require optic nerve sheath decompression. If headaches are severe and believed to be caused by increased ICP, CSF shunting procedures may be indicated.[2–4]
- Hydrocephalus may require surgical drainage using a shunt or third ventriculostomy.[2]
- For venous thrombosis, management is directed at reversing the underlying cause, controlling increased ICP and seizures, and anticoagulation.[5] The mainstay of treatment is anticoagulation with heparin or low-molecular-weight heparin followed by warfarin for 3 to 12 months.
- Meningitis treatment is directed at the underlying organism.
- Arteriovenous malformations may require surgical excision or embolization.

Prognosis

What is the prognosis?

The prognosis of papilledema depends on the underlying cause of the increased ICP.

In idiopathic intracranial hypertension, most patients with mild to moderate vision loss recover vision with treatment. About 80% have normal visual fields or mild residual visual field defects.[6] Vision loss can be progressive and severe in 4% to 6% of patients,[7,8] despite medical and surgical treatment. Recurrences may occur in 8% to 40% of patients.[2]

Venous thrombosis is associated with complete recovery or minimal residual signs in nearly 80% of patients. However, approximately 8% of patients die as a consequence of the venous thrombosis or the underlying condition.[9]

SUDDEN VISION LOSS

Epidemiology

What are the most common causes of sudden vision loss?

The most common causes of acute persistent vision loss are listed in **Box 3**.

History and Examination

Which elements in the history and examination are important in evaluation of sudden vision loss?

- Acuity of onset
- Chronicity of symptoms
- Severity of vision loss
- Pattern of symptoms
- Unilaterality or bilaterality
- Associated symptoms
- Past neurologic history, including history of strokes, seizures, migraines, and head trauma
- Ophthalmic history, including history of ocular trauma and surgeries
- Medical and past surgical history, including history of hypertension, diabetes, cardiovascular disease, arrhythmias, and rheumatologic disease

Associated symptoms can help determine the location of the lesion and guide the examination. For example, symptoms of headache, scalp tenderness, jaw claudication, polymyalgia rheumatica, or weight loss in an elderly patient are concerning for giant cell arteritis. Vision loss associated with new floaters and flashing lights is suggestive of retinal detachment.

Ocular causes of acute vision loss tend to be monocular, whereas optic nerve causes can lead to monocular or binocular vision loss, and lesions of the optic chiasm, radiations, and occipital lobe tend to cause vision loss in both eyes.

Ophthalmic examination, including measurement of visual acuity, pupil examination to assess for an afferent pupillary defect, slit lamp examination, and fundus examination, can identify ocular causes of vision loss and many lesions affecting the optic

Box 3
Common causes of acute persistent vision loss

Location of Lesion	Common Causes of Sudden Vision Loss
Ocular	Retinal detachment
	Macular degeneration
	Retinal artery occlusion
	Retinal vein occlusion
	Vitreous hemorrhage
	Angle closure glaucoma
Optic nerve	Ischemic optic neuropathy (atherosclerotic or arteritic)
	Inflammatory lesions (optic neuritis or sarcoidosis)
	Infiltrative process (neoplastic, infectious, or sarcoidosis)
Optic chiasm	Sellar mass
Optic tract	Aneurysm or other mass
Optic radiations	Stroke, neoplasm
Occipital lobe	Stroke or neoplasm

nerve. Formal visual field testing can help localize lesions affecting the optic chiasm and structures posterior to the chiasm.

Diagnosis

Which clinical findings and tests help guide a differential diagnosis?

Clinical features of key causes of acute vision loss are shown in **Box 4**.

Which radiographic imaging modalities are most useful?

Radiographic imaging modalities and appropriate diagnostic tests are listed by diagnosis in **Box 4**.

Management

Which patients should be hospitalized?

Patient with neurologic causes of sudden vision loss, such as pituitary apoplexy and acute stroke, require hospitalization. Most ophthalmic causes of sudden vision loss can be managed in an outpatient setting.

How should patients be managed in an inpatient setting?

- In acute stroke, the goals of initial management include stabilization of the patient, limiting neuronal injury, and re-establishing cerebral perfusion.[10] Intravenous recombinant tissue plasminogen activator (rtPA) is recommended for selected patients for treatment within 4.5 hours after the onset of stroke symptoms. Intra-arterial fibrinolysis may be considered for selected patients with major ischemic strokes within 6 hours of occlusion of the middle cerebral artery in patients who are not candidates for rtPA.[11]
- Vision loss caused by giant cell arteritis should be treated promptly with intravenous methylprednisolone 250 mg 4 times daily for 3 to 5 days, followed by oral prednisone therapy to prevent involvement of the second eye.[12]
- In patients with pituitary apoplexy, conservative management with steroid or other hormone replacement may be appropriate for stable patients without significant vision loss. Pituitary surgery may be indicated in patients with more significant neuro-ophthalmologic defects.[13]

Which patients require an inpatient ophthalmology consult?

Inpatient ophthalmology consultation should be obtained if the underlying cause of the acute vision loss has not been established.

How should patients be managed long-term?

- Retinal detachment usually requires surgical intervention with pars plana vitrectomy or scleral buckle placement.
- Maculopathies may require laser photocoagulation or intraocular injection of corticosteroids or anti–vascular endothelial growth factor agents.
- Angle closure glaucoma requires prompt administration of topical and systemic intraocular pressure lowering medications. Emergent laser peripheral iridotomy may also be required.

Box 4
Causes of sudden vision loss

Condition	Symptoms	Findings	Testing
Retinal detachment	New floaters, flashing lights, curtain	Retinal separation, reduced red reflex	Ophthalmologic consultation
Maculopathy (macular degeneration, macular hole, or hemorrhage)	Distortion or loss of central vision	Subretinal blood or fluid in macula	Ophthalmologic consultation
Retinal artery occlusion	Sudden monocular, painless loss of vision	Retinal whitening, ± cherry red spot in the macula	Ophthalmologic consultation. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) to assess for giant cell arteritis
Retinal vein occlusion	Sudden monocular, painless loss of vision	Retinal hemorrhages, dilated tortuous retinal veins	Ophthalmologic consultation
Vitreous hemorrhage	Black spots floating in vision, ± flashing lights	Mobile opacities (blood), reduced red reflex if substantial	Ophthalmologic consultation
Angle closure glaucoma	Red painful eye, nausea, vomiting, blurred vision, colorful haloes	Red eye, cloudy cornea, increased intraocular pressure	Ophthalmologic consultation
Ischemic optic neuropathy (atherosclerotic)	Sudden monocular, painless loss of vision	Afferent pupillary defect, ± optic disc edema	Ophthalmologic consultation. ESR and CRP to assess for giant cell arteritis
Arteritic ischemic optic neuropathy (giant cell arteritis)	Sudden severe loss of vision, age usually >60 y, initially unilateral but can become bilateral rapidly; ± headache, jaw claudication, scalp tenderness, neck pain, proximal muscle/joint pain, weight loss, anorexia, fever, diplopia	Afferent pupillary defect, pallid optic disc edema, temporal arteries may be prominent or tender	Increased ESR (may be normal in up to 22%), CRP, and platelets. Temporal artery biopsy should be performed within 1 wk of starting corticosteroids for definitive diagnosis
Optic neuritis	Vision loss typically in young adults. Vision loss over hours to days, may progress over 1–2 wk, and is frequently associated with pain with eye movements, loss of color vision	Afferent papillary defect, ± optic disc edema	MRI of the brain and orbits with gadolineum and fat suppression looking for white matter plaques (demyelinating lesions) or enhancement of the optic nerve

Sellar mass	Usually insidious or subacute vision loss	Bitemporal hemianopia, ± optic disc pallor	Visual field testing, enhanced and unenhanced MRI, serum prolactin, serum am cortisol, thyroid-stimulating hormone, thyroxine, luteinizing hormone, follicle-stimulating hormone, estradiol, or testosterone
Pituitary apoplexy (infarction or hemorrhage into a pituitary tumor)	Sudden and severe headache, stiff neck, nausea and vomiting, progressive vision loss, ± facial pain	± Ophthalmoplegia or ptosis; may have rapid neurologic deterioration, altered level of consciousness, endocrine deficiencies, possible death	MRI frequently shows a pituitary macroadenoma with heterogeneous signal. CT may show an unenhancing hyperdense lesion, or may miss the lesion
Occipital stroke or neoplasm	Sudden onset homonymous visual loss, ± focal weakness, numbness, difficulty with speech or gait	Homonymous hemianopia	CT or MRI

- In optic neuritis, treatment with intravenous methylprednisolone may be considered. The Optic Neuritis Treatment Trial[14] found that intravenous steroids accelerated the rate of visual recovery but did not improve the long-term visual outcome. Oral prednisone was associated with an increased rate of recurrences, and therefore is not indicated. Immunomodulatory medications may be considered in patients with MRI findings suggestive of multiple sclerosis.

Prognosis

What is the prognosis?

Prognosis is dependent on the cause of the vision loss.

- In giant cell arteritis, vision loss is typically severe and usually occurs as a result of ischemic optic neuropathy, retinal artery occlusion, or choroidal ischemia.[12,15] Both eyes may be involved simultaneously or sequentially. In 1 study, 54% had bilateral involvement, and the median time to involvement of the second eye was 5 days.[12] Visual recovery after giant cell arteritis is uncommon, but improvement in visual acuity may occur in 13% to 34% after treatment with corticosteroids.[12,16,17]
- In optic neuritis, recovery of vision usually begins within 2 weeks after onset of symptoms. Many patients have complete recovery of vision within 6 weeks.[14]

THIRD CRANIAL NERVE PALSY

Definitions

What is the definition of third cranial nerve palsy?

Third cranial nerve palsy refers to paralysis of the oculomotor nerve.

What is the function of the third cranial nerve?

The third cranial nerve innervates 4 extraocular muscles and the levator muscle of the eyelid. **Box 5** describes actions of the muscles innervated by the third cranial nerve. In addition, it also supplies parasympathetic fibers to the ciliary body to control pupil constriction and accommodation.

How are third nerve palsies classified?

Third nerve palsies are classified as being isolated or nonisolated.

- Isolated third nerve palsies are third nerve palsies without associated neurologic symptoms.
- A third nerve palsy is considered nonisolated in the presence of other neurologic signs such as hemiplegia, cerebellar signs, severe headache, other cranial nerve palsies, signs to suggest myasthenia gravis, or in the presence of signs of orbital disease.

Isolated third nerve palsies are further classified as complete or partial.

- In complete third nerve palsies, there is total dysfunction of the extraocular muscles and the levator palpebrae superioris.
- In partial third nerve palsies, there is variable dysfunction of the extraocular muscles and the levator palpebrae superioris.

Epidemiology

What are the most common causes of acquired third nerve palsy in adults?

The major causes of isolated third nerve palsy are shown in **Box 6**. In adults, the most common cause of third nerve palsy is vascular insufficiency caused by hypertension, atherosclerosis, or diabetes mellitus. The most feared cause of third nerve palsy is intracranial aneurysm, because it may be a sign of impending rupture.

Other less common causes include trauma, meningitis, stroke, and mass lesion at the base of the skull.[18]

Box 5
Actions of muscles innervated by the third cranial nerve

Muscle	Action
Superior rectus	Elevation
Inferior rectus	Depression
Medial rectus	Adduction (horizontal movement toward the midline)
Inferior oblique	Extorsion (outward rotation) and elevation

Box 6
Major causes of third nerve palsy in adults and children

Major Causes of Isolated Third Nerve Palsy in Adults	Major Causes of Isolated Third Nerve Palsy in Children
Ischemia	Congenital
Aneurysms (posterior communicating artery [PCOM], basilar artery, posterior cerebral artery [PCA])	Trauma
Tumors	Neoplasm
Trauma	Aneurysm

History and Examination

Which symptoms are associated with third nerve palsies?

- Sudden onset binocular horizontal, vertical, or oblique diplopia
- A droopy eyelid
- Pain (pain is common and is not helpful in distinguishing between causes)

What are the key clinical findings?

In complete third nerve palsies with pupil involvement:

- The eye is turned out and slightly down, with a paralysis of adduction, elevation, and depression.
- The pupil is dilated and unreactive.
- Ptosis is present.

In partial third nerve palsies (Fig. 2), there is variable dysfunction of the extraocular muscles; ptosis may be present.

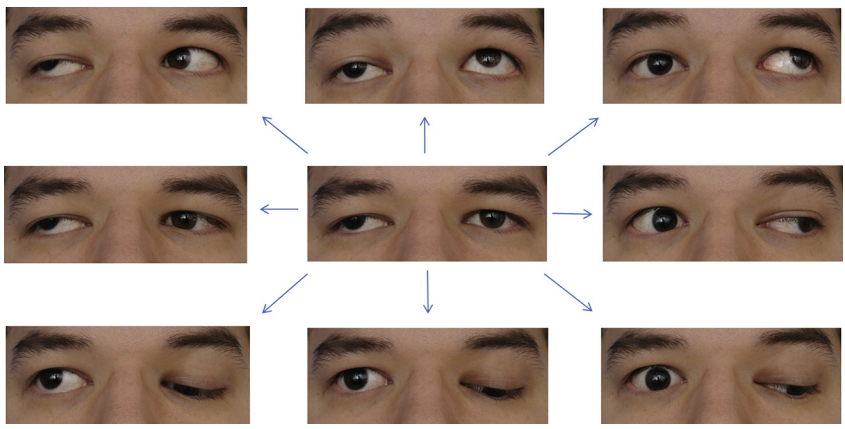

Fig. 2. Right third nerve palsy with pupil involvement, ptosis, and deficits of adduction, elevation, depression. The photographs also show evidence of aberrant regeneration, with eyelid elevation on downgaze and adduction.

Diagnosis

Which clinical findings help guide a differential diagnosis?

Lesions causing third nerve palsies may be located anywhere along the course of the third cranial nerve between the oculomotor nucleus in the midbrain and the extraocular muscles. Appropriate diagnosis and management depends on distinguishing those third nerve palsies in which the palsy is the only examination abnormality (isolated third nerve palsy) from those palsies in which other pertinent abnormalities, such as hemiplegia or a history of cancer, are also present (nonisolated third nerve palsy). **Box 7** lists causes of nonisolated third nerve palsy by location.

Brainstem lesions causing third nerve palsy are rare, and they are usually associated with neurologic deficits localizing to the midbrain. Lesions involving the oculomotor nucleus are associated with ipsilateral third nerve palsy with contralateral ptosis and superior rectus dysfunction. More rostral lesions may involve the pupil and spare eyelid function. Lesions of the oculomotor fascicles cause several syndromes associated with ipsilateral cerebellar ataxia (Nothnagel syndrome), contralateral cerebellar ataxia (Claude syndrome), contralateral tremor (Benedikt syndrome), or contralateral hemiparesis (Weber syndrome).[19]

Meningeal processes may cause third nerve palsies, which may be bilateral or occur in combination with other cranial nerve palsies, headache, neck stiffness, and altered mental status.

Cavernous sinus disease may manifest as dysfunction of any combination of the third, fourth, sixth, or seventh nerve, the first or second division of the fifth nerve, or Horner syndrome. Complete interruption of these nerves produces complete ophthalmoplegia, ptosis, and a dilated pupil; however, only 1 or 2 of the nerves within the cavernous sinus may be involved. Cavernous sinus lesion may also be associated with orbital signs, such as proptosis, periorbital swelling, chemosis, and conjunctival injection. Most cavernous sinus disturbances are caused by mass lesions.[20]

Orbital apex syndrome may cause third nerve palsy, often in association with fourth, fifth, and sixth nerve palsy, V1 sensory loss, and optic neuropathy from cranial nerve II involvement.[18]

ISOLATED THIRD NERVE PALSIES

Pupillary fibers travel superficially and superonasally on the third cranial nerve. They are therefore at risk for early involvement by compressive lesions, such as aneurysm or midline shift from uncal herniation. In isolated third nerve palsy, anisocoria of 2 mm or greater favors a compressive cause, such as aneurysm.

Anisocoria of less than 2 mm favors an ischemic cause,[21] but compressive lesions are still possible, particularly if the movements of the affected eye are only partially impaired. Aberrant regeneration is usually associated with recovery from acute third cranial nerve palsy caused by trauma or compressive lesions. This phenomenon is not typically found with ischemic third nerve palsies. Findings may consist of a constellation of symptoms. The most common is eyelid elevation (see **Fig. 2**) on downgaze or adduction (pseudo–von Graefe phenomenon).[22] Other findings may include pupil constriction with adduction, and unilateral globe retraction on upgaze or downgaze.

Which patients with third nerve palsy should undergo neuroimaging?

All adults with new-onset third nerve palsy should undergo neuroimaging.

Box 7
Causes of nonisolated third cranial nerve palsy by location

- Brainstem
  - Infarction
  - Hemorrhage
  - Neoplasms
  - Inflammation
  - Demyelination
- Subarachnoid space
  - Aneurysms (PCOM artery, basilar artery, PCA)
  - Infections
  - Neoplasms
  - Subarachnoid hemorrhage
  - Inflammation (eg, neurosarcoidosis, granulomatosis with polyangiitis)
  - Uncal herniation
- Cavernous sinus and superior orbital fissure disturbances
  - Neoplasms (expansion of pituitary masses, meningiomas, craniopharyngiomas, nasopharyngeal carcinomas, metastatic tumors)
  - Pituitary apoplexy
  - Inflammation (eg, Tolosa-Hunt syndrome, sarcoidosis)
  - Infection (paranasal sinus, skin, fungal, eg, mucormycosis, aspergillosis)
  - Cavernous sinus thrombosis
  - Carotid-cavernous sinus fistulas
  - Aneurysm
- Orbital apex
  - Neoplasms
  - Inflammation
  - Infections
  - Mucoceles
  - Trauma
- Generalized polyneuropathies (Guillain-Barré syndrome)
- Giant cell arteritis

In patients with nonisolated third nerve palsies with associated findings localizing to the brainstem, cavernous sinus, or orbital apex, MRI of the brain is indicated.

All patients with new-onset isolated third nerve palsy should undergo neuroimaging. Evaluation for a PCOM artery aneurysm should be performed emergently. CT angiography/CT is more sensitive to aneurysm,[23] more widely available, and faster than magnetic resonance angiography (MRA). Pregnant women and those with renal or cardiac failure should undergo emergent MRA/MRI.[24]

Which laboratory and diagnostic tests are helpful?

Patients older than 55 years should be evaluated for signs and symptoms of giant cell arteritis. If symptoms of headache, jaw claudication, scalp tenderness, neck pain, polymyalgia rheumatica, or vision loss are present, then ESR and CRP protein blood tests should be obtained.

If myasthenia gravis is suspected, acetylcholine receptor antibodies, repetitive testing, edrophonium testing, or single fiber electromyography may confirm the diagnosis. The ice test, sleep test, or neostigmine tests may also be considered.

In the presence of meningeal signs, such as headache, stiff neck, or altered level of consciousness, lumbar puncture should be performed after neuroimaging, if indicated. CSF examination, including cultures and cytology, should be performed to exclude bacterial, fungal, tuberculosis, syphilis, Lyme, sarcoidosis, carcinomatous, and lymphomatous meningitis.[18]

Management

Which patients should be hospitalized?

Most patients with acute-onset nonisolated third nerve palsy require hospitalization to manage the underlying cause of the third nerve palsy.

Which patients require inpatient ophthalmology consultation?

Inpatients with undiagnosed new-onset binocular diplopia require inpatient ophthalmology or neuro-ophthalmology consultation.

How should patients be managed?

Management of third nerve palsies varies by the location and type of the lesion. Intracranial aneurysms should be treated promptly, because death may occur if untreated. Management consists of surgical clipping, endovascular embolization, or less commonly, carotid occlusion.[18]

After treatment of the underlying cause, diplopia can be managed with occlusion of the affected eye or prisms. Once the palsy has stabilized, with consistent measurements for at least 6 to 12 months, strabismus surgery may be considered.

Prognosis

What is the prognosis?

Most patients with ischemic third nerve palsies recover spontaneously within 8 to 12 weeks.[25]

Treatment of an expanding but unruptured aneurysm by surgical or endovascular methods has a high chance of restoring the patient to normal neurologic health.[24] Ruptured intracranial aneurysms are associated with 66% mortality or a high chance of serious neurologic impairment.[26]

In third nerve palsies caused by PCOM artery aneurysms, complete third cranial nerve recovery is found in about 40% of patients and partial recovery in 50% after surgical repair. Surgical treatment within 14 days of onset of symptoms has been associated with a higher rate of complete third nerve recovery (64%) when compared with treatment more than 30 days after onset of symptoms (14%).[27]

ENDOGENOUS ENDOPHTHALMITIS

Definitions

What is the definition of endophthalmitis?

Endophthalmitis is an intraocular infection with involvement of the vitreous or aqueous humor.

How is endophthalmitis classified?

Endophthalmitis is classified as exogenous or endogenous.

- Exogenous endophthalmitis: intraocular infection resulting from inoculation of organisms from an external source. Exogenous endophthalmitis most commonly occurs after intraocular surgery or injections, trauma, or as a result of extension of local infection such as keratitis.
- Endogenous endophthalmitis: intraocular infection resulting from hematogenous spread of systemic infection, with spread to the eye.

Epidemiology

What is the incidence of endogenous endophthalmitis?

Endogenous endophthalmitis is less common than exogenous endophthalmitis, making up 2% to 8% of all cases of endophthalmitis.[28] Two retrospective chart reviews performed at tertiary-care medical centers had incidences of endogenous endophthalmitis of 1.8 cases/y over an 18-year period[29] and 3.2 cases/y over a 10-year period.[28]

What are the most common contributing comorbidities?

Predisposing medical conditions are usually present in patients who develop endogenous endophthalmitis.[28,30] Most cases occur in patients with other medical conditions, such as diabetes, gastrointestinal disorders (including gastrointestinal abscesses, recent endoscopy, or gastrointestinal surgery), cardiac disorders, or malignancy. Other risk factors include human immunodeficiency virus infection, dialysis, long-term use of broad-spectrum antibiotics, immunosuppressive therapy, major surgery, intravenous hyperalimentation, intravenous catheters, and intravenous drug use.[31–33]

Fungal endophthalmitis most commonly occurs in intravenous drug users and debilitated patients with predisposing factors of indwelling catheters, prolonged broad-spectrum antibiotic use, invasive procedures, and immunosuppression.[29,34]

An extraocular focus of infection is identified in 58% to 79% of patients.[29,33] In North America and Europe, the most common associations were with endocarditis, urinary tract infections, and meningitis. In East Asia, liver abscesses were the most common source, followed by pulmonary and urinary tract infections.[30]

What are the most common causative organisms?

Causative organisms vary significantly by geographic location.

- In the United States and Europe, the most common bacterial pathogens are gram-positive organisms, including *Staphylococcus aureus*, streptococci (primarily *Streptococcus pneumonia, S milleri*, and group A and B

streptococci).[28,29,33] Gram-negative bacilli such as *Escherichia coli* are responsible for about one-third of cases.[28]
- In Asia, endogenous endophthalmitis is most commonly cause by gram-negative organisms, with *Klebsiella pneumonia* being the most common microbe, in association with hepatobiliary infections.[30]

Fungal organisms are also an important cause of endogenous endophthalmitis. *Candida albicans* followed by *Aspergillus* and *Fusarium* are the predominant species.[31,34]

History and Examination

What are the key clinical features?

Patients with endophthalmitis frequently present with ocular symptoms, such as:

- Decreased vision
- Eye pain
- Redness of the eye
- Floaters
- Light sensitivity

Systemic symptoms, such as fever, chills, weight loss, or malaise, are reported less commonly and were reported in 57% to 82% of patients with bacterial endogenous endophthalmitis.[28,33] In 1 study, the physical examination was unremarkable, except for ocular findings in 41%.[29]

Examination findings may include:

- Decreased visual acuity
- Conjunctival hyperemia
- Eyelid edema
- Hypopyon (**Fig. 3**)
- Vitritis
- Reduced or absent red reflex caused by intraocular inflammation
- Increased intraocular pressure
- Retinal hemorrhages, white centered hemorrhages, or cotton-wool spots

Endophthalmitis may be bilateral in up to 26% of cases.[28–30,33]

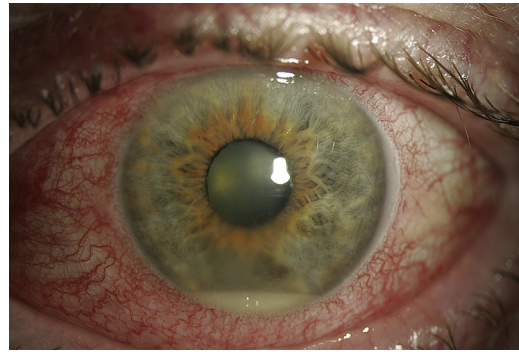

Fig. 3. Hypopyon and conjunctival hyperemia in endophthalmitis.

In cases of candidemia, *Candida* initially spreads hematogenously to the vascular choroid and to the retina, with subsequent extension into the vitreous cavity. It is the extension to the vitreous cavity that defines it as endophthalmitis.[34,35] Findings include creamy-white chorioretinal lesions (*Candida* chorioretinitis), which subsequently become associated with vitreous cells and fluffy white vitreous opacities (endophthalmitis) (Fig. 4).

Diagnosis

Which clinical findings help guide a differential diagnosis?

Endogenous endophthalmitis is frequently misdiagnosed,[28,29,33] leading to a delay in treatment. Endophthalmitis is most commonly misdiagnosed as noninfectious uveitis, conjunctivitis, acute glaucoma, or cellulitis.[33]

A high index of suspicion and a thorough history and examination are required for accurate diagnosis. History should include inquiry about:

- The duration and onset of symptoms
- Medical comorbidities, including diabetes, cardiac disease, hypertension, cancer, gastrointestinal disorders, chronic renal failure, and immunosuppression
- Recent hospitalizations
- Recent procedures including surgeries and endoscopies
- Recent trauma
- Use of antibiotics
- History of intravenous drug use

A detailed ophthalmologic examination including dilated fundus examination should be performed. In addition, general medical examination should be performed to identify any extraocular foci of infection.

Which laboratory tests are used to diagnose endophthalmitis?

In endogenous endophthalmitis, obtaining cultures is essential for appropriate management.

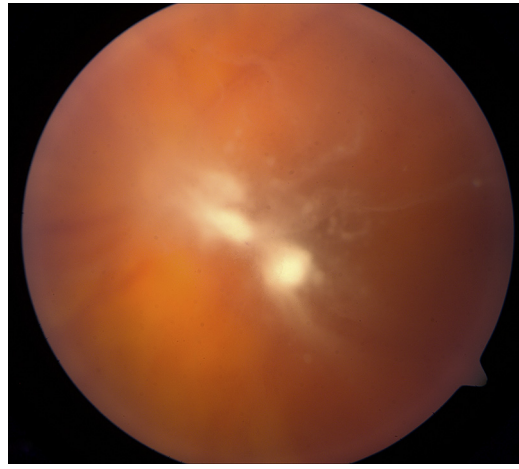

Fig. 4. Vitreous opacities in *Candida* endophthalmitis.

- Blood cultures can frequently confirm the diagnosis and were positive in 60% to 74% of patients with bacterial endogenous endophthalmitis.[28,33]
- Urine cultures were positive in 28% in 1 study.[28]
- CSF cultures may be performed as indicated by examination.
- Vitreous or anterior chamber sample should be obtained in all patients,[32] because this may be the sole source of microbial growth, especially in fungal endophthalmitis.[29,31]

Which other diagnostic tests are helpful?

In cases in which the source of infection is not immediately apparent, diagnostic tests such as transesophageal echocardiography to assess for endocarditis or CT of the abdomen to rule out gastrointestinal or other abscesses may be indicated based on examination findings.

In addition, ophthalmic ultrasonography may be helpful to rule out other conditions in the differential diagnosis, and to evaluate for associated conditions such as retinal and choroidal detachments.

Management

Which patients should be hospitalized?

Hospitalization should be considered in all patients with endogenous endophthalmitis for evaluation and management of the underlying cause of infection. In situations in which the patient is systemically well, such as in intravenous drug users, in whom transient bacteremia and fungemia may be the underlying cause, endophthalmitis may be managed in an outpatient setting.

How should patients be managed in an inpatient setting?

Systemic and intravitreal antibiotics are required for treatment of endogenous endophthalmitis.

The duration and type of systemic antibiotics are directed by the underlying source of infection and are frequently guided by cultures and sensitivities. In general, intravenous antibiotics are usually required for at least 2 weeks for most types of infections, or for at least 4 weeks in cases of endocarditis.[28]

Systemic antibiotics alone are usually insufficient to effectively treat the endophthalmitis. Although there are no randomized controlled trials for treatment of endogenous endophthalmitis, many advocate intravitreal antibiotics, especially when there is marked intraocular inflammation, because other routes of drug delivery frequently do not achieve satisfactory levels in the vitreous.[34] In most cases, empirical treatment is initiated before definitive culture results are obtained.

For bacterial endophthalmitis, vancomycin (1 mg/0.1 mL) in combination with ceftazidime (2.25 mg/0.1 mL) or amikacin (400 μg/0.1 mL) may be administered intravitreally. Surgical intervention with vitrectomy may be indicated in some cases to debride the vitreous, reduce pathogens and toxins, and obtain samples for culture.[31]

For fungal endophthalmitis, chorioretinitis with mild vitreous inflammation may be initially managed with systemic antifungal therapy and serial ophthalmologic examinations.[31,36] Systemic amphotericin B may be effective but has limited penetration into the eye. Voriconazole has good coverage against *Candida*, *Aspergillus*, and *Fusarium* and has good ocular penetration.[31] Vitrectomy, combined with systemic and intraocular

antifungals (amphotericin B 5–10 μg/0.1 mL or intravitreal voriconazole 100 μg/0.1 mL), is warranted in the presence of moderate or severe vitreous inflammation.[31,36,37]

Which patients require an inpatient ophthalmology consult?

- All inpatients suspected of having endophthalmitis should have urgent inpatient ophthalmology consultation.
- Patients with vision loss in the setting of a red, painful eye should also have inpatient ophthalmology consultation.
- Some recommend that dilated fundus examination should be performed on all patients with candidemia, greater than 1 week after onset of therapy.[38] Some studies have shown that ocular candidiasis or endophthalmitis can occur in up to 37% of patients with candidemia.[39] However, more recent prospective studies show that *Candida* chorioretinitis occurs in 9% to 16%, with endophthalmitis occurring in less than 2%.[35,38] The distinction between *Candida* chorioretinitis and endophthalmitis is important to make, because chorioretinitis without vitreous involvement usually responds to systemic antifungal therapy,[35,38] whereas endophthalmitis requires intravitreal antibiotics and sometimes vitrectomy.

Prognosis

What is the prognosis of endogenous endophthalmitis?

Effective treatment of endogenous endophthalmitis depends on early recognition and treatment, and virulence of the organism. Overall visual prognosis after endogenous endophthalmitis is poor, with more than 60% of patients with vision of hand motion or worse. About 25% of patients require evisceration or enucleation[28,33] in cases of bacterial endophthalmitis. Visual outcomes in *Candida* endophthalmitis are better than outcomes of endophthalmitis caused by bacteria or molds.[29] The worst outcomes typically occur in endophthalmitis caused by streptococci, *Bacillus* species, and molds.[34]

Performance Improvement

Endogenous endophthalmitis is a rare disease, with potentially devastating consequences. Effective treatment is dependent on early recognition. Endophthalmitis may occur in the inpatient setting or present in outpatient clinics to ophthalmologists or primary care physicians. Endogenous endophthalmitis is misdiagnosed about half of the time,[28,29,33] which can lead to a delay in treatment. Hospitalists, primary care physicians, ophthalmologists, and other care providers must have a high index of suspicion to ensure timely diagnosis and treatment.

CLINICAL GUIDELINES

There are no clinical guidelines for management of papilledema, third cranial nerve palsies, or endogenous endophthalmitis.

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