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INTRINSIC NEOPLASMS

In the previous chapter, the organization of axons in the sensory visual system provided the basis for understanding the patterns of visual field defects. In this chapter, the neuroanatomy of the anterior sensory visual system forms the foundation for understanding optic nerve disorders and their clinical expression.

ANATOMY

The optic nerve originates from the confluence of ganglion cell axons as they traverse the scleral canal to exit the eye, and ends anatomically as these axons merge with the axons of the fellow optic nerve at the chiasm. Anatomic divisions of the optic nerve include intraocular, intraorbital, intracanalicular, and intracranial portions.

INTRAOCULAR COURSE

The short intraocular course of the optic nerve is often referred to as the optic nerve head, and the portion that can be seen with the ophthalmoscope is called the optic disc. The optic disc is a pink oval measuring about 1.5 by 1.75 mm, with its long axis oriented vertically. In most subjects, the optic cup, devoid of axons, is seen centrally, surrounded by the pink, doughnut-shaped neuroretinal rim. The rim consists of axons end-on, as they pass from the nerve fiber layer

and make a right-angled turn into the scleral canal. Although the number of axons in normal subjects is relatively constant, the diameter of the scleral canal may vary among individuals. When the scleral opening is small, the axons seem crowded into a small space. These small cupless discs are often referred to as "discs at risk," because they are frequently associated with optic disc infarction (anterior ischemic optic neuropathy [AION]). Individuals with large scleral openings may have large discs with large central cups, which can simulate the pathologic cupping characteristic of glaucoma.

Optic nerve axons congregate into bundles as they pass through thelamina cribrosa. This fibrous diaphragm is contiguous with the sclera and has 200 to 300 openings. The lamina cribrosa further divides the intraocular optic nerve head into prelaminar, laminar, and postlaminar portions. Optic disc edema occurs when the prelaminar axons swell from blockage of orthograde axoplasmic flow at the level of the lamina cribrosa. Axoplasmic stasis and disc swelling can be caused by many of the optic nerve disorders discussed in this chapter and is not disease-specific.

Just behind the globe, two to six short posterior ciliary arteries (branches of the ophthalmic artery) penetrate the sclera in a circumferential fashion around the optic nerve. These vessels form an incomplete anastomotic ring at the level of the choroid (Zinn-Haller), supplying both the high-flow vasculature of the choroidal circulation and the optic nerve head. Although the central retinal vessels pass through the optic nerve head, their contribution to its vascular supply is negligible (Fig. 4-1). Insufficient blood flow through the posterior ciliary arteries from thrombosis, hypotension, or vascular occlusion resulting from arteritis can cause optic nerve head infarction (i.e., AION).

INTRAORBITAL COURSE

After passing through the lamina cribrosa, the retinal ganglion cell axons acquire myelin sheathing, doubling the diameter of the optic nerve to greater than 3 mm. The myelin sheath is produced byogliodendrocytes, the same cell type in the white matter tracts in the central nervous system. Peripheral nerves are myelinated by Schwann cells. Thus the optic "nerve" is histologically a white matter tract rather than a peripheral nerve. This fact accounts for the frequent occurrence of optic neuritis in demyelinating disorders of the central nervous system, such as multiple sclerosis.

The orbital portion of the optic nerve is approximately 25 mm in length from the posterior aspect of the globe to the orbital apex. Because the globe is only 15 mm anterior to the orbital apex, the optic nerve describes a gently curved path; the extra length allows full movement of the globe without tethering by the optic nerve. In the orbit, the optic nerve is surrounded by the optic nerve sheath, which is continuous with the intracranial dura through the optic canal posteriorly and bounded by the sclera anteriorly. The sheath encloses an extension of the intracranial meninges: with

pia, arachnoid, and cerebrospinal fluid continuous with the intracranial cavity. Elevated intracranial pressure can be transmitted directly to the optic nerve head, causing bilateral optic disc edema (papilledema). Meningiomas can arise within the orbit from the optic nerve sheath, just as they occur from the intracranial meninges.

At the orbital apex, the nerve sheath fuses with a fibrous ring (annulus of Zinn) that forms the insertion of the superior, inferior, and medial rectus muscles. This connection explains why eye movement can cause pain when the optic nerve is inflamed in retrobulbar optic neuritis.

The vascular supply of the intraorbital optic nerve is more robust than that of the optic nerve head. Branches of the ophthalmic artery serve numerous longitudinal pial vessels on the surface of the optic nerve, which in turn yield penetrating vessels that extend toward the center of the nerve. The central retinal artery enters the nerve about 10 mm behind the globe, also contributing to the vascular supply of the proximal intraorbital optic nerve. Given such a hardy blood supply, ischemic insults to the retrobulbar optic nerve are rare, in contrast to the frequent occurrence of optic disc infarction (i.e., AION).

Intracanalicular Course

The intracanalicular portion of the optic nerve is about 10 mm long; beginning where the optic nerve enters the optic foramen in the lesser wing of the sphenoid, and ending at the point where the optic nerve exits the optic canal and enters the intracranial cavity. From the orbit, the optic canal moves medially and superiorly to enter the intracranial cavity. The optic canal is separated from the sphenoid sinus by very thin bone, and the course of the optic nerve can be seen as a convexity in the lateral wall of the sinus. In addition to the optic nerve, the optic canal also contains the ophthalmic artery.

Space-occupying lesions within the bony confines of the optic canal do not have to be large to compress the intracanalicular optic nerve and cause visual loss (intracanalicular meningioma), and may not be easily seen on neuroimaging. Blunt trauma to the orbital rim can transmit forces to the optic canal, causing optic nerve contusion and/or canal fractures. Subsequent edema within this confined space may produce additional ischemic injury.

Intracranial Course

The intracranial portion of the optic nerve is approximately 15 mm long, extending from the nerve's entrance into the intracranial cavity to the chiasm, but this measurement may vary greatly depending on the relative location of the chiasm. The optic nerves angle superiorly at 45 degrees from the skull base and converge toward the midsagittal plane to form the chiasm. The anterior clinoid is superior and lateral to the optic nerve as the nerve emerges from the optic

foramen. The frontal lobes and olfactory tracts are above the nerve. The vascular supply of the optic nerve in this location includes the carotid arteries, located laterally, as well as the anterior cerebral arteries and the anterior communicating arteries, located superiorly. As the carotid artery emerges from the cavernous sinus, the ophthalmic artery originates, traveling on the inferior surface of the optic nerve to enter the optic foramen. Carotid-ophthalmic artery aneurysms or dolichoectatic atherosclerotic enlargement and displacement of the carotid artery can cause compression of the intracranial optic nerve.

CLINICAL EXPRESSION OF DISEASE

Optic nerve disorders commonly produce pallor, pathologic cupping, or swelling of the optic disc.

PALLOR AND CUPPING

The axons that make up the optic nerve may be affected by disease anywhere along their course, from their origin in the inner retina to their synaptic endpoint in the lateral geniculate body. Fatal injury to an axon results in retrograde and orthograde degeneration of the axon and eventual death of the retinal ganglion cell of origin. Axonal injury remote from the optic disc may cause optic nerve dysfunction without any acutely observable optic disc abnormality, but over time, optic disc atrophy and nerve fiber layer dropout in the inner retina become visible, revealing the extent of the damage. In most neuro-ophthalmic disorders, axonal loss manifests as pallor of the normally pink neuroretinal rim, without apparent loss of neuroretinal rim mass. Diffuse disc pallor is a final common pathway for many optic neuropathies and is nondiagnostic. However, the location of segmental pallor is often instructive, such as the sectorial or altitudinal pallor in AION, "bowtie" atrophy in optic tract (or chiasmal) lesions, or temporal pallor characteristic of the toxic/nutritional or hereditary optic neuropathies. Loss of axons may also manifest as optic nerve cupping as the central cup enlarges from axonal dropout. Optic disc cupping is characteristic of glaucoma, but can occur in other optic neuropathies. Cupping with pallor of the remaining neuroretinal rim suggests a cause other than glaucoma.

OPTIC DISC SWELLING (EDEMA)

Swelling of the prelaminar axons causes elevation and expansion of the optic nerve head. The normally distinct border of the optic disc becomes blurred as swollen peripapillary axons become elevated and less transparent. Axons swell when the normal process of axoplasmic flow is "dammed up" by mechanical or ischemic processes. Transudation of fluids from injured axons and disc vessels is also a contributor to the disc's swollen appearance (Fig. 4-2). Many different insults to the optic nerve can result in optic disc swelling (Box 4-1). Elevated intracranial pressure, transmitted

to the nerve head within the confines of the optic nerve sheath, can cause stasis of axoplasmic flow at the level of the lamina because of regional pressure differentials. Ischemic optic neuropathy produces optic disc swelling as a result of ischemia. Inflammation from infection or demyelination can also produce disc swelling. The history, examination, and clinical course help to determine the diagnosis. Important features in developing a differential diagnosis are listed in Fig. 4-3, with individual disorders covered in detail in the sections that follow.

Infiltration of the optic nerve head by cancer cells, inflammatory cells, and/or infectious organisms is another mechanism of optic nerve head elevation. Generally, these processes also incite concomitant optic disc swelling.

Some anomalous, but otherwise normal, optic discs may be elevated, giving the false appearance of optic disc edema (Box 4-2).

Accompanying Signs

Rapid expansion of the optic disc from edema can cause damage to the optic disc and peripapillary vasculature, resulting in hemorrhages at many levels: deep, dark peripapillary subretinal hemorrhages; dot/blot intraretinal hemorrhages; nerve fiber layer hemorrhages (usually flame-shaped); and (rarely) vitreous hemorrhages. Vascular changes can include telangiectasia on the disc surface (increased "capillarity") or venous stasis (increased venous caliber). Telangiectasis on the disc and of the peripapillary vessels can accompany Leber's hereditary optic neuropathy (LHON). Collateral ("shunt") vessels on the disc can be seen in optic nerve sheath meningioma or compensated retinal vein occlusion. An increase in the diameter of the intraocular portion of the optic nerve from axonal swelling produces concentric peripapillary chorioretinal folds, called "Paton's lines" (see Fig. 4-2). Macular choroidal folds, oriented radial to the disc, frequently occur as a result of indentation of the posterior globe by the optic nerve sheath expanded by high cerebrospinal fluid pressure, but can also occur in Graves' disease or from an orbital mass. Macular edema can occur from massive disc edema of any cause but is most frequently seen accompanying optic disc edema in infectious processes ("neuroretinitis").

ISCHEMIC OPTIC NEUROPATHIES

As its name implies, anterior ischemic optic neuropathy (AION) is the result of ischemia. The designation ofanterior implies that the ischemic insult causes damage to the optic nerve head that is visible with the ophthalmoscope. AION is thought to be caused by occlusion of one or more of the short posterior ciliary arteries that supply the optic nerve head.Nonarteritic AION is common and is most likely the result of vascular insufficiency from thrombosis and/or hypotension in patients with atherosclerotic disease. A more devastating form of AION is caused by

vasculitic occlusion of the supply arteries from giant cell arteritis. Arteritic AION can cause bilateral blindness, as well as significant systemic morbidity related to vasculitic arterial closure.

The term posterior ischemic optic neuropathy (PION) suggests an infarct of the optic nerve beyond the optic disc, with a normal-appearing nerve initially. PION is rare and is not a well-defined clinical entity. It occurs almost exclusively in the setting of vasculitis.

Nonarteritic Anterior Ischemic Optic Neuropathy

Nonarteritic AION is a common cause of sudden, painless, monocular visual loss in patients after the fourth or fifth decade of life (Fig. 4-4). Systemic hypertension (40%) and/or diabetes mellitus (20%) is commonly present. Frequently, patients have other systemic manifestations of atherosclerotic disease such as angina pectoris, previous myocardial infarction, or history of stroke.

Symptoms

Visual loss in this condition ranges from profound to mild and is frequently first noted by patients when they awaken from sleep. The visual loss is generally painless but can be associated with a mild ocular ache. Patients may have a stepwise decline in vision over several days, but the visual deficit is usually stable after onset. A subset of patients (5-10%) have a relentlessly progressive stepwise decline in vision for weeks following the initial event.

Signs

The visual field loss is commonly a mix of central and altitudinal visual field defects, but any disc-related visual field defect can occur (Fig. 4-4, A). Not uncommonly, patients are specific in their histories, stating that they "have lost the lower (or upper) half of vision." Occasionally, central acuity is spared, but the vast majority of the time, the visual field defect includes fixation.

The optic disc edema may be diffuse or segmental. For example, a dense inferior altitudinal visual field defect may be associated with segmental swelling of the superior pole of the optic disc, with relative preservation of the inferior pole (Fig. 4-4, B). The discs are commonly small and cupless "discs at risk," a finding that may only be appreciated by viewing the contralateral (unaffected) optic disc (Fig. 4-4, B). This finding is so universal that patients who have moderate or large cup-to-disc ratios should be considered to have some other process (such as arteritic AION) until proven otherwise. Peripapillary nerve fiber hemorrhages frequently accompany the disc edema. The remainder of the fundus is generally unremarkable, although retinal arterioles may reflect systemic hypertension,

diabetes, or atherosclerotic disease. The disc swelling generally resolves within 3 to 6 weeks, leaving optic disc pallor (Fig. 4-4, C-D).

Causes

Nonarteritic AION is thought to be a stroke of the optic nerve head, resulting from insufficient blood flow through the posterior ciliary arteries. Atherosclerosis that accompanies aging, or that is accelerated by systemic vascular diseases such as hypertension and diabetes, narrows the lumen to a critical level where thrombosis or even mild hypotension results in ischemia. The crowded optic discs commonly identified in these patients may initiate and perpetuate a cascade: ischemia causing edema, edema in the narrow confines of the crowded disc causing further ischemia from increased tissue pressure, with a downward spiral of increasing edema and ischemia.

The timing of this ischemic event characteristically occurring at night and in the early morning may be explained by nocturnal hypotension (Hayreh, 1994). Systemic blood pressure is normally lower at night when patients are sleeping. Hypertension (and other vascular disorders) can damage arterial compliance and local autoregulation, such that nocturnal hypotensive swings can reach a critical level that precipitates AION. Long-acting antihypertensive medications may further accentuate nocturnal hypotension. Not infrequently, patients who present with AION report having been changed to stronger or longer-acting antihypertensive medication in the weeks or months before the event. Obviously, withdrawal of the patient's antihypertensive medications is not the answer, but it is reasonable to suggest to the patient's medical physician that long-acting antihypertensives be taken in the morning or that shorter-acting drugs be considered.

Differential diagnosis

The most important consideration in the differential diagnosis is distinguishing nonarteritic AION from arteriticAION caused by giant cell arteritis (see Fig. 4-3). In every case of AION, the clinician should ask specific questions regarding the systemic symptoms of vasculitis (see following section). AION may be difficult to distinguish from optic neuritis in patients 35 to 45 years old, and these patients may need to have both possibilities investigated.

Evaluation

A sedimentation rate, C-reactive protein, and complete blood count should be drawn in most cases to address the possibility of an arteritic cause. Syphilis is a rare but treatable cause, and serologic tests for this disease should also be routine. Patients without known diabetes or hypertension should be assessed for these two diseases. Patients who are

younger than 50 years old without known risk factors require serologic evaluation for vasculitis (rheumatologic studies), infection, or hypercoagulable states (Box 4-3).

Neuroimaging is generally not indicated as long as the history is convincing for AION (sudden onset, stable course), and the examination is consistent (optic disc edema). If optic neuritis is a consideration, an MRI may be needed to assess the possibility of multiple sclerosis. Patients who present with recent visual loss and optic nerve pallor may require neuroimaging to evaluate for possible compressive neuropathy (such as a meningioma, parasellar or sellar tumor, or Graves' orbitopathy).

Treatment

No proven, effective treatment is available for nonarteritic AION. Obviously, underlying precipitating factors should be addressed, such as blood loss, anemia, or factors inducing hypotension. As previously discussed, a patient's medications for systemic hypertension should be reviewed with the medical physician. Oral steroids and high-dose intravenous steroids might theoretically be beneficial but have not been convincingly proven to help in this disorder. The use of optic nerve sheath fenestration in this condition was explored by the Ischemic Optic Neuropathy Decompression Trial (IONDT). The study suggested that this surgery was not beneficial and may even be harmful. The use of a daily aspirin may decrease the risk of an event in the contralateral eye (see following section).

Clinical course

Patients should have repeat visual field tests taken after several weeks and after several months to ensure that the visual field loss is not progressive. Once nonarteritic AION has finished its course and optic pallor ensues, this process is unlikely to occur again in the same eye. One proposed rationale for this lack of recurrence is that the death of axons from an ischemic event "frees up" space for the remaining axons, effectively reversing the crowding of the optic disc. About one half of patients with nonarteritic AION may experienceminimal improvement in visual function with time, usually manifest as slight improvement in visual acuity (Fig. 4-4,E). The incidence of occurrence in the fellow eye may be as high as 50 to 60%, although it generally occurs years later. Simultaneous or sequential events in both eyes should raise strong suspicions of a vasculitic cause (i.e., giant cell arteritis). Unlike retinal vascular events, the life expectancy of patients with nonarteritic AION is not significantly shortened.

ARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY (GIANT CELL ARTERITIS)

Arteritic AION is caused by vasculitic closure of the posterior ciliary arteries from giant cell arteritis. The visual loss is usually more profound than nonarteritic AION and may occur in both eyes at the same time or in rapid succession. Patients with giant cell arteritis are usually more than 60 years old, and the disease becomes more common with each decade of life (Fig. 4-5). Arteritic AION is unusual before age 60, and only a few cases of patients with this diagnosis in their forties have been documented. Among patients with giant cell arteritis, females outnumber males 3 to 1.

Causes

Giant cell arteritis is an idiopathic systemic vasculitis consisting of inflammation in the wall of small and medium-sized arteries, usually involving the extracranial arteries of the head. The inflammatory products may greatly expand the wall thickness, obliterating the lumen of the vessel and obstructing blood flow with resultant ischemic consequences.

Symptoms

Patients with giant cell arteritis may present with rapid and profound blindness from ischemic optic neuropathy in one or both eyes. Permanent visual loss is frequently preceded by transient visual loss lasting minutes, similar to amauroses fugax (see Table 1-3). Although the visual loss itself is painless, patients commonly complain of headache, scalp tenderness, and jaw claudication. Scalp tenderness may be caused by tenderness over inflamed arteries or may be secondary to scalp ischemia. Scalp tenderness may be so intense that patients complain of pain when lying on a pillow, combing their hair, or wearing a hat. Ischemia to the muscles of mastication result in jaw pain (claudication) with chewing or in tongue pain. Additional manifestations of this systemic vasculitis include weight loss, poor appetite, general malaise, myalgia, arthralgia, and low-grade fever.

Polymyalgia rheumatica (PMR) is a chronic rheumatologic disorder characterized by proximal shoulder and buttocks pain without tenderness. PMR may be a precursor or concomitant accompaniment of giant cell arteritis.

Signs

Visual field defects from arteritic AION may be similar to those found in nonarteritic AION, although the visual acuity and field are frequently much more severely affected. Not uncommonly, patients present with NLP vision. The optic disc appearance may be indistinguishable from nonarteritic AION, but more commonly, it is diffusely edematous and pale (Fig. 4-5, A). On occasion, arteritis can cause a "posterior" ischemic optic neuropathy (PION), in which the

optic disc appears normal or is only minimally affected acutely. Acute, profound visual loss in an elderly patient with an unimpressive disc and retina or visual loss that exceeds the observed optic disc edema strongly suggest giant cell arteritis (Box 4-4). Bilateral or rapidly sequential AION also requires immediate consideration of vasculitis. In contrast to nonarteritic AION, glaucomatous-like optic disc cupping may develop following arteritic AION.

The occasional occurrence of a retinal infarct in the distribution of a cilioretinal artery in the setting of AION is highly suggestive of arteritis. This association is not surprising because the optic disc and peripapillary choroid share a common blood supply--the short posterior ciliary arteries.

Inflamed temporal arteries (or other scalp arteries) can frequently be palpated as a firm "cord" with a poor or absent pulse, explaining this disorder's alternate name: temporal arteritis. Fortunately, these frequently involved arteries are also easily surgically accessible for biopsy.

Forty percent of patients with giant cell arteritis have visual loss. If the disorder is unrecognized and untreated, visual loss in the second eye can occur in 65% of patients with arteritic AION, usually within several weeks. Early recognition of this process is vital to prevent bilateral blindness. Other vascular consequences of giant cell arteritis are listed in Box 4-5.

Differential diagnosis

The evaluation of cases presenting as AION is directed at determining whether the process is arteritic or nonarteritic as discussed in the following section (see Fig. 4-3). Fluorescein angiography has been advocated by some experts as a potential way of distinguishing these two entities. Patients who have profound narrowing of the posterior ciliary arteries resulting from giant cell arteritis demonstrate areas of choroidal hypoperfusion on the early sequences of IVFA, with a marked delay in choroidal filling (Fig. 4-6).

Patients with bilateral arteritic AION can be distinguished from acute papilledema by the degree of visual loss, which is severe in AION and is usually minimal or absent in acute papilledema.

Elderly patients with acute, profound visual loss but with minimal disc or retinal changes may have PION from giant cell arteritis; other entities in the differential diagnosis are listed in Box 4-4.

Evaluation

Although no pathognomonic laboratory test is available for identifying giant cell arteritis, an elevated Westergren erythrocyte sedimentation rate (usually above 50) and elevated C-reactive protein add weight to the clinical suspicion of this disorder. Liver enzymes may be elevated as well. The erythrocyte sedimentation rate (ESR) is a nonspecific

indicator of inflammation and is also elevated in patients with infectious, collagen-vascular, renal, or neoplastic disorders. The normal sedimentation rate increases with age. The upper limit of normal for a given age can be estimated by dividing the age by two in males and by adding ten before dividing by two in females. Anemia is common, and a low hematocrit tends to elevate the ESR further. However, the ESR may be normal in up to 10% of patients who have giant cell arteritis.

A definitive diagnosis can only be made by identifying characteristic pathologic features in a biopsy of an affected artery (see Fig. 4-5, C and D). A temporal artery biopsy should be performed on all patients suspected of having giant cell arteritis, even those patients in whom the clinical diagnosis seems certain. A positive biopsy may not change the short-term treatment plan, but it is invaluable in managing patients in the months and years following the diagnosis, particularly if they develop significant systemic morbidity related to steroid therapy.

The vasculitis in giant cell arteritis is not continuous and may be found in patches along an artery with normal or healing intervening areas. Therefore, temporal artery biopsies should be at least 2 to 3 cm in length because a short biopsy specimen, or one that is not completely serially sectioned, may miss the pathologic area. A single arterial specimen is diagnostic in 80 to 90% of patients who have giant cell arteritis. Most clinicians advocate a biopsy of the contralateral temporal artery or other symptomatic scalp artery if the initial temporal artery biopsy is negative. Biopsy of two sites increases the sensitivity to more than 90%. Some clinicians biopsy the temporal artery on both sides during the same surgery.

Thus a patient suspected of having giant cell arteritis should have an ESR and C-reactive protein drawn, and steroids should be immediately administered (see following section). A temporal artery biopsy should be performed within 1 to 2 weeks of beginning steroids because the rate of a positive biopsy falls over several weeks as the steroids reverse the inflammatory changes. After months of treatment, discontinuities of internal elastic lamina may be the only pathologic finding, suggesting "healed" arteritis.

The clinical presentation, ESR, C-reactive protein, and temporal artery biopsy are usually sufficient to establish a definitive diagnosis. In atypical cases, neuroimaging may be required, and the differential diagnoses outlined in Fig. 4-3 and Box 4-4 will need to be addressed. Giant cell arteritis is by far the most common vasculitis causing ischemic optic neuropathy in patients more than 50 years old, but occasionally, laboratory studies may be needed to address other vasculitides such as systemic lupus erythematosus, polyarteritis nodosa, rheumatoid arthritis, or herpes zoster.

Treatment

The prompt administration of steroids may prevent bilateral blindness--an outcome that is not uncommon when diagnosis or treatment is delayed. In patients with acute visual loss, high-dose intravenous steroids may actually recover some vision. A common regimen is 250 mg of intravenous methylprednisolone (Solu-Medrol) every 6 hours over several days. This treatment may require hospitalization based on the age and potential for medical complications in these patients, but it can be given in an outpatient or home healthcare setting. Patients without acute visual loss but with clinical suspicions of arteritis should be started immediately on 60 to 80 mg of oral prednisone daily until a biopsy can be performed.

Patients with giant cell arteritis may require oral steroids for 1 year or more. Most patients can be tapered to lower doses over a period of months by careful monitoring of their sedimentation rate, C-reactive protein, and symptoms. Collaboration with the patient's medical doctor is of paramount importance, given the potential systemic complications of steroid therapy. Occasionally, alternative immunosuppressive therapies such as methotrexate may be effective as a steroid-sparing agent (particularly in diabetic patients).

DIABETIC PAPILLOPATHY

Diabetic patients with optic disc edema may have diabetic papillopathy (diabetic papillitis) (Fig. 4-7). This condition has features that suggest it is clinically different from typical nonarteritic AION: (1) the patients are younger (15-40), (2) visual field defects are less severe, (3) the condition is often bilateral, and (4) the visual deficits are more likely to improve with time. The optic disc edema is usually diffuse rather than focal, and the discs display a fine diffuse telangiectasia that may be difficult to distinguish from neovascularization. When it is bilateral, diabetic papillitis may mimic papilledema (often referred to as "diabetic pseudopapilledema"). Diabetic papillitis and AION may be indistinguishable in some cases. The precise cause of diabetic papillitis is uncertain, but it likely represents a form of optic nerve head ischemia. No known effective treatment is available. Steroids have been advocated, but this therapy in diabetic patients frequently produces medical complications and is of unproven efficacy.

PAPILLOPHLEBITIS

Papillophlebitis is a poorly defined cause of unilateral optic disc edema that occurs most commonly in healthy patients who are 20 to 30 years old (Fig. 4-8). Patients present with painless, mild visual loss. The optic disc shows diffuse hyperemic disc swelling, with dilated veins and flame-shaped peripapillary hemorrhages. The optic disc appearance suggests a central retinal vein occlusion (CRVO), but the hemorrhages do not extend far from the disc and

are not found in the retinal periphery. This entity is most likely a variant of CRVO, and the clinical evaluation may need to be the same as CRVO in a young person: assessment for hypercoagulable states (see Box 4-3).

OPTIC NEURITIS

Optic neuritis typically causes acute monocular visual loss in young adults aged 15 to 45, associated with pain induced or worsened by eye movement (Fig. 4-9). Incidence in females outnumbers males 5 to 1. The term optic neuritis literally suggests any condition that causes inflammation of the optic nerve. However, most clinicians reserve this term for primary demyelinating events such as the optic neuropathy associated with multiple sclerosis or idiopathic conditions that have a similar clinical course.

Symptoms

Optic neuritis usually causes monocular visual loss, described by patients as a haze, cloud, or dimness with poor color vision. The visual loss may progress over 2 to 7 days, at which point the vision begins to slowly improve, with normal or near-normal visual function often achieved over several weeks or months (Fig. 4-9, F). Retro-ocular pain, made worse with eye movement, usually precedes visual symptoms and continues during the phase of visual decline. As previously discussed, the pain likely originates from extraocular muscle traction on an inflamed optic nerve at the annulus of Zinn. Occasionally, patients report seeing brief spots of light (phosphenes, photopsias) induced with eye movements or by loud sounds. A neurologic history and review of symptoms may reveal previous or concomitant neurologic events that suggest a diagnosis of multiple sclerosis, such as transient episodes of numbness, weakness, loss of bowel or bladder control, or persistent imbalance.

About one half of patients with active or recovered optic neuritis may note dimming of vision in the affected eye when their body temperature is elevated, such as after exercise, after a shower or sauna, or with a fever. This transient visual loss is called Uhthoff's phenomenon and results from temporary impairment of optic nerve function, which may be caused by elevated body temperature or changes in the pH or ion content of the blood.

Signs

Visual acuity is usually affected. Color vision deficiencies may be more severe than would be predicted from visual acuity alone. Potential visual field defects include any optic-disc-related visual field abnormality. Although a central scotoma is the classic finding, altitudinal visual field defects are also at least as common, making the distinction between this disorder and AION difficult in certain cases. Finding slight visual field abnormalities in the asymptomatic

eye is not unusual. The RAPD frequently seems to be measurably larger than expected from the visual field defect. However, patients who have had optic neuritis in the fellow eye may have a minimal or absent RAPD. Even after a patient's visual acuity, visual field, and color vision have recovered, the RAPD tends to persist, as does the brightness sense disparity between an affected and unaffected eye.

The prolonged conduction velocity of an affected optic nerve can be demonstrated as a delay (increased latency) in the signal generated with VEP testing. This test is not useful in the diagnosis of optic neuritis in a symptomatic eye because common clinical tests of visual function present more compelling evidence of a previous or current optic neuritis. However, VEP testing is frequently employed by neurologists seeking evidence of demyelination at multiple sites in nonocular, monosymptomatic patients with suspected multiple sclerosis. The Pulfrich phenomenon (see Chapter 2) may be observed by patients with unilateral optic neuritis, as a direct consequence of delayed signal velocity in an affected optic nerve.

The optic disc initially appears normal in two thirds of patients, suggesting that the demyelinating event is posterior to the optic nerve head. The remaining one third of patients demonstrates optic disc swelling that is usually diffuse and mild, occasionally with a few associated disc and nerve fiber layer hemorrhages (Fig. 4-9,B). The macula is unaffected, unlike the macular edema or edema residues seen in neuroretinitis. With time, optic disc pallor becomes evident in all patients but may be subtle. Optic disc pallor can sometimes be seen in an asymptomatic eye, suggesting a previous subclinical optic neuritis. Uveitis and peripheral retinal venous sheathing have been described in some patients with multiple sclerosis.

Causes

The presumed cause of optic neuritis is an autoimmune attack on the myelin coating of the optic nerve, rather than the axons themselves. The myelin internodes allow rapid signal conduction (saltatory conduction). Loss of the myelin component in the optic nerve dramatically affects vision because the transfer of visual information is slowed when saltatory conduction breaks down. With time, incomplete repair occurs and function returns to near-normal. This is the same process of myelin damage that occurs in the myelinated white matter tracts in the brain with multiple sclerosis. A high percentage of patients with optic neuritis will eventually have other areas of white matter affected, yielding a diagnosis of multiple sclerosis.

Differential diagnosis

The differential diagnosis in young patients with recent profound visual loss, a large RAPD, and a normal optic disc is a relatively short list consisting of optic neuritis and a series of other less likely disorders (see Box 4-4). Compressive optic neuropathy is possible in such patients, but the necessity of neuroimaging in patients with optic neuritis (see following section) addresses this potential diagnosis. A longer list of potential causes must be considered in those patients with disc swelling, including AION, LHON, and infiltrative and infectious neuropathies (see Fig. 4-3).

Evaluation

The Optic Neuritis Treatment Trial (ONTT) was a national, prospective, randomized study directed at the effects of treatment on optic neuritis. In considering a multitude of clinical tests in young patients presenting with classic optic neuritis, the ONTT established that neuroimaging was the only helpful test in determining treatment. As will be discussed in the following section, the presence of other white matter plaques suggests treatment with high-dose intravenous steroids (Fig. 4-9, D). An MRI of the brain and orbits with gadolinium should be obtained to address treatment considerations, evaluate for systemic multiple sclerosis, and look for any unexpected findings (such as an optic nerve sheath meningioma). MRI of the orbits with fat suppression often demonstrates variable enhancement of the involved optic nerve (Fig. 4-9, C) but may be normal.

Treatment

The ONTT randomized 455 patients with optic neuritis into three treatment groups: (1) no treatment (placebo tablets), (2) moderate-dose oral prednisone, and (3) high-dose IV methylprednisolone for 3 days (followed by oral prednisone for 11 days). The outcomes of the study and resultant treatment recommendations are outlined in Table 4-1.

Patients in the intravenous steroid group in the ONTT were admitted to hospital and were treated with 250 mg of intravenous methylprednisolone every 6 hours for 3 days, followed by an 11-day oral prednisone taper. Many clinicians have modified this regimen to make it practical for home intravenous therapy, administering 500 mg of methylprednisolone twice a day, or even 1000 mg daily, for 3 to 5 days.

Another consideration in determining who to treat includes any underlying medical conditions that would present a significant risk to the patient with steroid use. Complications from intravenous steroid therapy in the young, otherwise healthy subjects in the ONTT were rare but included transient psychosis, elevated blood sugar, and acute pancreatitis.

Clinical course

The ONTT demonstrated that 90% of patients improved within one year to 20/40 or better, regardless of treatment. Subjective and objective improvement in the visual field should be evident in 3 to 5 weeks after onset (Fig. 4-9, E-F). Failure to improve is still compatible with a diagnosis of optic neuritis, but at that point, other items in the differential diagnosis should be considered. A continued, relentless decline in vision over months is not typical for optic neuritis and requires reinvestigation, often with repeat views of the orbit and optic nerve with MRI or CT.

Steroid-dependent optic neuropathies improve while a patient is on steroids but worsen when the steroids are stopped. This pattern is far more typical of inflammatory processes or neoplasia than of optic neuritis, and additional investigation should be directed accordingly (Box 4-6).

Patients with white matter plaques on MRI or other neurologic symptoms in addition to visual loss should be evaluated by a neurologist for multiple sclerosis. Sixty to eighty percent of females with optic neuritis, and a lower percentage of males, eventually develop clinically diagnosable multiple sclerosis in their lifetimes (Box 4-7). The diagnosis of multiple sclerosis requires symptoms or signs of at least two lesions separated in space (anatomic location) or time. Among patients with a definitive diagnosis of multiple sclerosis, virtually all can be shown to have optic nerve dysfunction (for example with VEP), but only one half of these patients have had a symptomatic event.

Variations

Optic neuritis can occur in response to a viral illness or immunization, or may be "idiopathic," with a presentation and course identical to the optic neuritis associated with multiple sclerosis but without ever manifesting systemic symptoms.

Children may present with bilateral optic disc edema and visual loss, presumably from a postinfectious optic neuritis or meningoencephalitis. These cases are not generally associated with a risk of development of multiple sclerosis. Symptomatic bilateral optic neuritis in adults is unusual, although the optic neuritis treatment trial demonstrated minimal visual field defects in the asymptomatic eye of many patients with optic neuritis. Devic's disease is a variant of multiple sclerosis consisting of bilateral optic neuritis with lower extremity weakness and paresthesia from upper spinal cord demyelination usually occurring in children and young adults (see Fig. 1-1).

PAPILLEDEMA

The term papilledema means swelling of the papilla (optic disc). However, the term is generally reserved to describe bilateral optic disc edema that results from elevated intracranial pressure.

Mechanism of Papilledema

Cerebrospinal fluid (CSF) is produced by the choroid plexus in the lateral ventricles, flowing through the midline third ventricle and cerebral aqueduct to the fourth ventricle. From the fourth ventricle, CSF flows through the foramina of Magendie and Luschka into the subarachnoid space surrounding the brain and spinal column, as well as into the orbital extension of the subarachnoid space bounded by the optic nerve sheath. CSF is absorbed by the arachnoid granulations into the adjacent superior sagittal sinus.

High CSF pressure in the brain is conveyed through the optic canal into the space bounded by the optic nerve sheath in the orbit, increasing tissue pressure within the optic head, inducing stasis of axoplasmic flow. Axoplasmic stasis causes swelling of prelaminar axons, resulting in optic disc swelling. Secondarily, compression of the venous structures within the nerve head leads venous engorgement and capillary dilation with hemorrhage. Trabeculations exist between the optic nerve sheath and pia of the optic nerve, and vary between individuals in their impedance to transmission of CSF between the brain and the orbit. Variation in sheath anatomy may account for the marked asymmetry or unilaterality of optic disc edema, or (rarely) the absence of disc edema in patients with intracranial hypertension.

Elevation of the superior sagittal sinus venous pressure (venous sinus thrombus, dural AVMs, right heart failure, radical neck dissection) reduces CSF absorption and may cause intracranial hypertension. Damage or malfunction of the arachnoid granulations (meningitis, subarachnoid hemorrhage, toxins or drugs) or obstruction of ventricular outflow (aqueductal stenosis, tumor) can also raise CSF pressure (Table 4-2). Expanding brain tumors are obviously one of the more worrisome causes of papilledema.

Although many of the causes of intracranial hypertension are evident on neuroimaging, a significant group of patients have normal neuroimaging (Box 4-8). Idiopathic intracranial hypertension (pseudotumor cerebri) refers to a group of predominantly obese females with elevated intracranial pressure and papilledema without an obvious cause.

Idiopathic Intracranial Hypertension (Pseudotumor Cerebri)

Idiopathic intracranial hypertension (IIH) is a condition of unknown cause that produces elevated intracranial pressure and papilledema, primarily in obese females between puberty and menopause. Neuroimaging is essentially normal, without tumor or identifiable obstruction of the ventricular system (Box 4-9). The female-to-male ratio of patients with IIH is about 8 to 1. Obesity is present in more than 90% of females with this disorder (Fig. 4-10).

The terminology surrounding this condition is somewhat confusing and imprecise. This clinical disorder is often called pseudotumor cerebri, but this term technically includes any condition other than tumor that causes intracranial hypertension. Use of the termbenign intracranial hypertension (BIH) raised objections because the condition can occasionally have severe visual consequences. The designation idiopathic intracranial hypertension seems to clearly define the clinical group discussed here, but in some cases a potential cause can be implicated with reasonable certainly and the disease may not qualify as truly idiopathic (see Box 4-8). The best suggestion is to use the term IIH for the idiopathic condition discussed in this section, unless an identifiable cause can be named to complete the designation, such as "intracranial hypertension secondary to vitamin A toxicity."

Symptoms

The most common symptom associated with IIH is headache, although in some cases it can be conspicuously absent. Often, patients note that the headache is more painful with bending over or with coughing. Another frequent finding is pulsatile tinnitus, often described as "hearing a swishing heartbeat" in one or both ears. Patients describe brief episodes of unilateral or bilateral visual loss with postural changes, typically lasting seconds, calledtransient visual obscurations. The phenomenon is most likely related to deficient maintenance of perfusion of the swollen optic nerve head with even slight changes in blood pressure. Permanent visual loss may occur if the optic disc swelling becomes chronic. Marked engorgement of the optic nerve sheath can also flatten the posterior aspect of the globe. This condition can produce blurred vision as the result of macular choroidal folds or can create a hyperopic shift in the patient's refraction by shortening the axial length of the eye. Transient or lasting horizontal diplopia may occur from associated sixth cranial nerve dysfunction.

Important concerns in the patient's history include medications taken over the previous year, weight gain or loss, head trauma, symptoms of sleep apnea, and any previous intracranial or head/neck surgery. Vitamin A consumption by tablet or diet (liver, fad diets) should be assessed. Menstrual irregularities are common in females in this age group, so their reported association with IIH is tenuous at best.

Signs

The appearance of optic disc swelling may be variable. The classic appearance is a diffuse, uniform elevation of the optic disc that gives it a "champagne cork" appearance. Nerve fiber layer hemorrhages and deep peripapillary retinal hemorrhages are common (Fig. 4-10,A). The optic disc edema is often asymmetric between the two eyes, and occasionally is unilateral. Not infrequently, distinguishing anomalous optic discs from true edema may be difficult (see

Box 4-2). Patients with optic disc edema reportedly lack the normal pulsations of the central retinal vein at the optic disc. However, at least one third of normal discs lack pulsations, so their absence is a "soft" sign at best.

Visual function is relatively normal with early disc swelling. Expansion of the optic disc and the resulting lateral and upward displacement of the peripapillary retina produce both relative and absolute enlargement of the blind spot on formal perimetry. Over time, chronic disc swelling and ischemic damage causes axonal death and optic atrophy, producing visual field defects. Nasal steps are the most common defect seen initially (Fig. 4-10, B), with concentric depression of the entire visual field in advanced stages. Central vision is rarely affected until late in the course (or with acute fulminant disc swelling); thus visual acuity alone is of little help in assessing the disease's progress. Rarely, central vision can be affected by an associated peripapillary choroidal neovascular membrane and subretinal hemorrhage, choroidal folds, or macular edema.

Elevated intracranial pressure does not seem to damage intracranial structures, and neurologic deficits apart from visual loss should raise suspicion of some other disorder. The single exception to this rule is sixth cranial nerve paresis. Presumably, changes in intracranial pressure (and the brain's position in the cranium) may stretch and injure the sixth cranial nerves, given their firm attachment to the brainstem and to the skull base.

Causes

In IIH, there is no overt structural obstruction to the circulation of CSF. Convincing studies have shown that the problem lies in defective reabsorption of CSF at the level of the arachnoid granulations. The association of this condition with certain medications is consistent with this idea because toxins could potentially interfere with the active transport mechanisms required for CSF absorption by the arachnoid granulations (see Box 4-8).

The role of obesity in this disorder is unclear, but it seems to be a causative factor because IIH often resolves with weight loss alone. Many investigators have suspected a hormonal mechanism related to lipid metabolism. IIH may be associated with sleep apnea, a disorder that is also more common in obese patients.

Differential diagnosis and evaluation

The differential diagnosis of bilateral disc elevation is found in Fig. 4-3. The most important entities to address in the differential diagnosis of papilledema include brain tumors, obstruction of the ventricular system, or dural-sinus thrombosis. For this reason, neuroimaging should be performed immediately. Although a CT scan is capable of ruling out an intracranial mass, an MRI with contrast is superior to CT in imaging venous-sinus thrombosis, arteriovenous malformations, and infiltrating tumors (Fig. 4-11). Blood pressure should be measured (with appropriate-sized cuffs)

on all patients because malignant hypertension may present with bilateral disc edema (Fig. 4-12). In addition, patients with intracranial hypertension and systemic hypertension may have a poorer visual prognosis. Abrupt lowering of blood pressure in either circumstance (IIH or malignant hypertension) may precipitate acute, severe, permanent visual loss.

Truly idiopathic intracranial hypertension is uncommon in males. Some males with this initial diagnosis have been discovered to harbor occult dural arteriovenous malformations, have sleep apnea, or have other identifiable causes of papilledema.

Baseline automated perimetry (such as Humphrey 30-2 or 24-2) and optic disc photographs should be performed because these parameters are the most reliable indicators of disease progression and treatment effectiveness.

A lumbar puncture must be performed to make the diagnosis of IIH, even when the clinical presentation is classic. In addition to documenting the opening pressure, CSF can be examined for evidence of hemorrhage, infection, or neoplasm. The opening pressure is measured in the lateral decubitus position with legs and head in a relaxed position. Opening pressures greater than 250 mm confirm the presence of intracranial hypertension; pressures between 200 to 250 mm are suggestive but less certain. Only rarely are additional lumbar punctures of any utility. This procedure is not an effective form of treatment because the CSF volume is quickly regenerated. Lumbar puncture is also not a reliable way of monitoring the effectiveness of medical treatment because CSF pressure has marked hour to hour fluctuations.

Diagnosis and treatment of this disorder are best performed when an ophthalmologist and neurologist work together. The ophthalmologist follows the important indicators of disease and the potential for lasting morbidity--the visual fields and disc appearance. The neurologist's role is to confirm the diagnosis with a neurologic examination and lumbar puncture, and to help in the medical management of headache.

Treatment

Treatment alternatives include observation, diet, medication, and surgery. Patients without significant visual field defects may not require medical or surgical treatment, especially if a suspected precipitating cause has been eliminated, such as vitamin A or antibiotics, patients recovering from meningitis or head trauma, or obese patients in a successful weight loss program.

Acetazolamide (Diamox) reduces intracranial pressure by decreasing CSF production. This drug is generally effective when given in doses of 500 mg twice a day, often with convincing improvement in 3 to 4 weeks (see Fig. 4-

10). Side effects include paresthesias of extremities and face, dysgeusia (especially with carbonated beverages), and dyspepsia. Fortunately, serious side effects, including anaphylaxis, aplastic anemia, and Stevens-Johnson syndrome, are extremely rare. Furosemide (Lasix) is less effective in the treatment of this disorder. Steroids may be helpful, but the inevitable weight gain associated with steroid use is counterproductive. Short-term, high-dose intravenous steroids may be useful in fulminant cases.

An optic nerve sheath fenestration or neurosurgical shunting procedure (ventriculoperitoneal or lumboperitoneal shunt) may be required for patients with progressive visual field loss despite medical therapy. Optic nerve sheath fenestration effectively reduces the transmitted CSF pressure at the optic disc by opening the sheath, thereby allowing CSF to be diverted into the intraconal tissues for absorption. Optic disc edema is reliably reversed by this procedure, but its long-term effectiveness is uncertain. The CSF pressure (as measured by lumbar puncture or intracranial monitor) is not affected by optic nerve sheath fenestration, but clinicians have reported improvement in patients' headaches and in the appearance of the contralateral disc in some patients. However, patients with severe headaches that are unresponsive to vigorous medical treatment may benefit most from a neurosurgical shunt.

Clinical course

Frequent, formal visual field tests are required to follow the course of a patient with chronic papilledema because visual acuity may remain 20/20 despite severe peripheral visual field loss. Serial observations of the optic discs and perimetry are required regardless of the treatment because treatment failures may occur at any time. Shunt failure may occur without causing headache and may produce insidious peripheral visual loss that may go unnoticed until visual loss is severe and damage to the optic disc is irreversible.

The majority of patients respond well to Diamox, with resolution of optic disc edema over 3 to 6 months. When the optic disc edema is gone, a trial period off Diamox with careful observation is reasonable, especially if the patient has been successful with weight loss. Some patients never have a recurrence, while in others the condition is a chronic, lifelong problem.

Other Causes of Papilledema

Because many of the signs and symptoms of elevated intracranial pressure involve the eyes, the ophthalmologist is often the first physician to encounter patients with intracranial tumors, dural-sinus thrombosis, and other neurologic or neurosurgical conditions. Many of these conditions are diagnosed when the ophthalmologist investigates papilledema with neuroimaging. Obviously, prompt referral to the appropriate specialist is the most important course of

action. However, the ophthalmologist still has an important role in the multidisciplinary management of such patients because his or her serial observations of optic disc appearance and visual fields often determine the therapeutic course.

COMPRESSIVE OPTIC NEUROPATHIES

Mechanical compression of the optic nerve can cause axonal death or demyelination without permanent axonal injury. Ischemia also plays a major role in the pathogenesis of compressive neuropathies because tumors can disrupt local perfusion by mechanical pressure or "steal" the blood supply. Unlike other cranial nerves, optic nerve axons do not regenerate after a lethal injury. However, successful reversal of optic nerve (or chiasmal) compression can result in significant improvement in visual field defects, presumably from recovery of demyelinated and partially injured axons. Prompt diagnosis is therefore important, as early intervention may offer the best chance for visual recovery.

OPTIC NERVE SHEATH MENINGIOMA

Optic nerve sheath meningiomas are a cause of unilateral progressive visual loss, most common in females (female-to-male ratio of 3 to 1) in their fourth decade of life (Fig. 4-13). Meningiomas of the optic nerve sheath represent 5% of all orbital tumors and 1% of all meningiomas (most are intracranial).

Symptoms and signs

Patients describe an insidious, painless loss of vision in one eye. Any type of optic-nerve-related visual field defect can occur. A classic pattern seen with Goldmann perimetry is a central scotoma that gradually connects (or "breaks out") to the periphery. Proptosis may develop, depending on the bulk and location of the meningioma. Diplopia can occur if the tumor restricts free movement of the globe. Rarely, gaze-dependent amaurosis can occur as compression of the optic nerve or its vascular supply is induced with eccentric gaze.

The classic triad of findings with optic nerve sheath meningiomas includes (1) disc pallor, (2) optic disc collateral vessels, and (3) progressive visual loss; however, not all of these elements are invariably present. The optic nerve may be pale or edematous, depending on the location and duration of the lesion. Retinociliary venous vascular collaterals ("optociliary shunts") on the optic disc occur in response to obstruction of central retinal venous outflow. Neuroimaging may show thickening of the nerve/nerve sheath complex. CT imaging of the orbits often shows enhancement of the sheath, which spares the nerve itself, appearing as a "railroad track" on axial images and as a "bull's eye" on coronal views.

Causes

Optic nerve sheath meningiomas arise from the meningeal components of the optic nerve sheath in the orbits. Similar to intracranial meningiomas, the tumor rarely metastasizes but causes local injury by compression of adjacent structures. In the orbit, the tumor tends to encircle the optic nerve, causing injury by myelin displacement, axonal disruption, or compromise of the optic nerve's blood supply. Some meningiomas have hormone receptors, with potentially massive growth when exposed to exogenous hormones or the high levels of progesterone and estrogen produced during pregnancy.

Variations

Optic nerve sheath meningiomas may extend into the optic canal or may originate from the dura within the optic canal. The confines of the canal may allow a small meningioma to cause marked compression of the optic nerve that may be difficult to visualize on neuroimaging. Meningiomas arising from the orbital sheath often extend through the optic canal and into the intracranial cavity. Meningiomas can also arise from the intracranial dura, compressing the intracranial optic nerve or the chiasm. Sphenoid wing meningiomas commonly have intraorbital and intracranial components. These tumors can also extend laterally, producing a characteristic "filling in" of the temporal fossa that can be palpated on examination.

Unlike adults, meningiomas in children tend to be aggressive and often result in death.

Differential diagnosis and evaluation

The triad of pallor, optic disc shunt vessels, and progressive visual loss can also be present with sarcoidosis or optic nerve glioma. Optic nerve sheath meningiomas can also produce a disc appearance similar to retinal vein occlusions; vein occlusions can produce shunt vessels similar to those seen with optic nerve sheath meningiomas, meningiomas can secondarily produce an element of venous stasis, and both conditions may cause disc edema. The optic disc edema and visual field loss from optic nerve sheath meningioma may initially look similar to ischemic optic neuropathy or optic neuritis, but a slow, relentless decline in vision is highly suggestive of a compressive optic neuropathy (Fig. 4-13, F).

Neuroimaging is required when a compressive optic neuropathy is suspected, either with an MRI of the brain and orbits (with contrast and orbital fat suppression) or CT imaging of the brain and orbits with contrast (including true coronal orbital cuts). Sometimes, the enlarged appearance of the nerve may be difficult to distinguish from optic nerve glioma or inflammatory conditions such as sarcoidosis or optic neuritis. Performing both MRI and CT may narrow the

diagnosis and aid in assessing the intracranial extent of growth. In some cases, biopsy of the mass is required to make a diagnosis and plan treatment. Meningioma biopsies should be analyzed for estrogen and progesterone receptors.

Treatment

Excision of an optic nerve sheath meningioma invariably strips the vascular supply of the optic nerve, resulting in blindness. Thus patients with useful vision are generally not candidates for surgical excision. Surgical excision of an optic nerve sheath meningioma is usually only considered when the tumor is confined to the orbit and the eye is blind. The decision to excise a tumor when intracranial extension is present is complex and depends on (1) whether the contralateral optic nerve or chiasm is threatened; (2) the size, location, and growth of the tumor; and (3) remaining sight in the affected eye. Radiation therapy for optic nerve sheath meningiomas is currently emerging as a viable treatment option.

The effectiveness of medical treatment generally depends on the hormonal responsiveness of the tumor. Tamoxifen, an estrogenic competitive inhibitor, and mifepristone (RU486), an antiprogesterone agent, may slow the growth of selected receptor-positive meningiomas. Steroids have only a short-term effect.

Observation may be the only reasonable initial "treatment." Although biopsy may confirm the diagnosis, histologic appearance does not correlate well with biologic behavior. The natural history of optic nerve sheath meningiomas is highly variable; they may remain static for many years or they can progress relatively rapidly. Careful monitoring of optic nerve function in patients with optic nerve sheath meningioma is vital because it provides a guide for management. Tumor progression is evaluated by monitoring visual fields, visual acuity, contrast sensitivity, color vision, and RAPD, as well as repeat neuroimaging.

ORBITAL DISORDERS

Orbital Graves' disease can cause compression of the optic nerve by marked enlargement of the extraocular muscles. The manifestations of Graves' disease are discussed in detail in Chapter 8. However, a compressive optic neuropathy can occur even in the absence of the external signs of Graves' disease (see Fig. 8-4).

Space-occupying lesions in the orbits, such as capillary hemangiomas, orbital varices, mucoceles, metastatic tumors, fibrous dysplasia, or infectious cysts, can also present as compressive optic neuropathies.

INTRINSIC NEOPLASMS

Optic Nerve Glioma

Optic nerve gliomas occur primarily in children; 75% of patients present before age 20 (Fig. 4-14). Decreased vision may be the presenting complaint, but strabismus and nystagmus resulting from poor vision may often be noted first by the child's family. Proptosis can occur, depending on the extent and bulk of orbital involvement.

About one half of optic nerve gliomas arise in the orbital portion of the optic nerve, with the remainder arising intracranially. Fifty percent of patients with optic nerve gliomas have neurofibromatosis type I. Fifteen percent of patients with neurofibromatosis type I harbor an optic nerve glioma.

Pathologically, the tumor is a pilocytic astrocytoma (juvenile type), with a benign cytologic appearance. In children, the tumor enlarges slowly or may appear inactive. Gliomas of the anterior visual pathway that arise in adulthood behave differently, exhibiting malignant behavior and rapidly leading to blindness and death (Fig. 4-15).

Neuroimaging of childhood gliomas typically reveals a fusiform swelling of the optic nerve and/or chiasm. Involvement of the chiasm may be associated with endocrine dysfunction and hypothalamic involvement, necessitating an endocrine evaluation in all children with optic nerve or chiasmal glioma. As previously discussed, a pediatric evaluation for systemic signs of neurofibromatosis is also required.

Treatment is controversial, but most clinicians favor a conservative "watch and wait" approach given the usual static course in children. Surgical resection may be considered in patients with a blind eye and disfiguring proptosis or isolated orbital involvement. Indications and effectiveness of radiation treatment or chemotherapy are uncertain.

Lymphoproliferative Disorders

Neoplastic involvement of the optic nerve may present with grotesque infiltration and elevation of the optic nerve head, or as an initially normal-appearing disc that gradually turns pale from a retrobulbar process. Acute leukemic infiltrative optic neuropathy is a true oncologic emergency because prompt radiation treatment may be sight-saving (Fig. 4-16). Infiltrative optic neuropathies should be considered in patients with visual loss and a known lymphoproliferative disorder, patients who are systemically ill, or those whose history and examination do not fit the patterns of common optic neuropathies. Infectious (such as tuberculosis) and inflammatory (sarcoidosis) entities may be infiltrative in nature and should be considered in the differential diagnosis (Box 4-10). In addition, patients whose optic neuropathy improves with steroids only to worsen when steroids are stopped ("steroid-dependent" neuropathy)

may have an infiltrative optic neuropathy (see Box 4-6). MRI of brain and orbits with contrast may show optic nerve enhancement or other intracranial foci.

INFLAMMATORY OPTIC NEUROPATHIES

Inflammation of the optic nerve can be caused by many processes. Primary idiopathic inflammatory optic neuropathies include sarcoidosis (Box 4-11) and orbital inflammatory pseudotumor (discussed in Chapter 8). Inflammation accompanies infectious, neoplastic, autoimmune, and other optic neuropathies, making it difficult to categorize the primary disease process (Box 4-10).

INFECTIOUS OPTIC NEUROPATHIES

OPTIC DISC EDEMA WITH A MACULAR STAR

Optic disc edema with a macular star (ODEMS) is a descriptive term that includes several different disease processes, characterized by the presence of optic disc edema and macular edema. The termneuroretinitis is often used interchangeably with ODEMS, but neuroretinitis has come to specifically imply an infectious cause.

Noninfectious entities that often produce coexistent disc and macular edema include hypertensive retinopathy, and postoperative cystoid macular edema (Irvine-Gass syndrome). Hypertensive retinopathy is invariably bilateral with other retinal signs (see Fig. 4-12), and cystoid macular edema does not usually develop a "star." Exudative lesions in the retinal periphery (Coats' disease, capillary hemangiomas) can cause macular stars, but the disc is usually unaffected. Diabetic maculopathy, occasionally accompanied by diabetic papillopathy or optic disc neovascularization, tends to produce circinate edema residues and is not likely to be confused with this entity. Macroaneurysms of retinal vessels near the disc can cause macular exudates and optic disc edema. Optic disc edema from any cause, when extreme, may be associated with macular edema and a "star." This observation suggests that all causes of disc edema may need to be considered in the differential diagnosis of ODEMS when the degree of optic disc swelling is extreme.

The precise pathophysiology of infectious neuroretinitis is not known, but it likely involves an exudative process in the vessels of the disc and macula triggered by the infectious agent or the subsequent immune response to the agent. The availability of sensitive serologic tests for the etiologic agent in cat-scratch disease (Bartonella henselae) demonstrates that this organism is a common cause of neuroretinitis. Other organisms that can cause neuroretinitis includeToxoplasma gondii, syphilis, Lyme disease, and viral entities. A bilateral, recurrent, idiopathic neuroretinitis with a poor visual outcome has been described (Purvin, 1994).

CAT-SCRATCH NEUORETINITIS

Patients with neuroretinitis from cat-scratch disease (CSD) are typically young people or children who develop a febrile illness several weeks after exposure to a kitten (Fig. 4-17). The disease is transmitted by a scratch from an infected cat, or may be transmitted by fleas from the cat to the human.

Symptoms

The systemic symptoms include fever, malaise, and general adenopathy that usually resolve after 1 or 2 weeks. Only a small percentage of patients with CSD develop neuroretinitis and visual loss. Visual symptoms usually begin 2 to 3 weeks after the systemic symptoms have subsided. Many patients do not recall an antecedent systemic illness. The examiner should question the patient specifically about fever, malaise, cough, adenopathy, exposure to cats and kittens, as well as known or potential sexually transmitted diseases when appropriate.

The time course of visual loss is similar to optic neuritis, as it may progress over several days and tends to improve over several months. Pain with eye movement can occur but not nearly as frequently as with optic neuritis.

Signs

Central and cecocentral scotomas are the most common visual field defect. The visual deficit generally cannot be accounted for by the maculopathy alone, suggesting optic nerve dysfunction as well. As with optic neuritis, color vision defects and the presence of an RAPD are present.

The optic disc shows mild to moderate diffuse edema, frequently with a focal elevation of the optic disc that has the appearance of an optic disc granuloma. The optic disc edema is accompanied by white edema residues in the inner macula that line up radially in Henle's layer, forming a star. Acutely, the macular edema may be subtle and the patient may be thought to have optic neuritis. Usually, within a week or so of the onset of visual symptoms, the characteristic edema residues in the macula appear. The radial star pattern may completely encircle the fovea or may be limited to only one sector. A few vitreous cells may be present. Deep, white, choroidal patches are occasionally seen in the retinal periphery, even in the fellow asymptomatic eye (Fig. 4-17, C).

Evaluation

Patients with a classic history and examination may not require an extensive evaluation. All patients should have blood pressure measured because macular stars can occur in hypertensive retinopathy. Laboratory studies that may be helpful include a complete blood count with differential, toxoplasmosis titer, and syphilis and Lyme disease serologies.

A positive serologic titer (IFA) for Bartonella henselae is specific and thus may be helpful in confirming the suspected cause. However, a negative titer does not exclude CSD.

Treatment

The visual prognosis for CSD neuroretinitis is good, with most patients experiencing a significant recovery regardless of treatment. This natural history of recovery makes it difficult to assess the efficacy of treatment. Many clinicians treat CSD neuroretinitis with a course of ciprofloxacin, doxycycline, or other antibiotics.

OTHER INFECTIOUS NEUROPATHIES

Infectious agents can affect the optic nerve (1) by direct infiltration of the optic nerve by the organism, (2) by inciting a local inflammatory response or autoimmune attack on the optic nerve, (3) by local mass effect from an infectious focus, or (4) by compromise of the vascular supply by vasospasm or vascular occlusion from the products of an inflammatory response. Many agents have been implicated (see Box 4-10), but syphilis can affect the visual pathway in so many varied ways that it should be included in the differential in most forms of optic neuropathy.

TOXIC AND NUTRITIONAL OPTIC NEUROPATHIES

Slow, bilateral, and symmetric loss of central vision is characteristic of toxic and nutritional optic neuropathies. Toxins and nutritional deficiencies are usually grouped together for two reasons: (1) in many cases, they are both present as co-conspirators causing an optic neuropathy, and (2) toxins and nutritional deficiencies produce clinical findings that are essentially identical.

Visual fields reveal bilateral cecocentral scotomas (Fig. 4-18). The optic discs may appear normal but frequently show temporal pallor. Careful observation may reveal nerve fiber layer dropout in the papillomacular bundle. Common causes discussed in the following paragraphs include alcoholism, ethambutol toxicity, and vitamin B_{12} deficiency. Additional causes are listed in Box 4-12.

Alcoholism is a common cause of toxic/nutritional optic neuropathy. The nutritional deficiencies that inevitably accompany alcoholism may be the most damaging factor, but a toxic effect of alcohol and its byproducts may also play a role. Most patients demonstrate remarkable improvement with vitamin supplementation, particularly with folate and thiamine. Referral to a substance abuse specialist is needed to prevent the cycle of alcohol abuse and nutritional deprivation from repeating. The combination of alcoholism and cigarette smoking may have synergetic optic nerve toxicity ("tobacco-alcohol amblyopia").

Ethambutol is commonly used to treat tuberculosis and atypical mycobacterial infections. Toxicity to the optic nerve may occur at a previously tolerated dose when other toxic agents are added to a patient's regimen or when weight loss from the chronic infection increases the dose per kilogram of body weight. Stopping the medication usually allows slow improvement of the patient's vision, often taking several months.

Pernicious anemia from malabsorption of vitamin B_{12} may be difficult to diagnose because the optic neuropathy may occur before a significant anemia and macrocytosis develop. Testing for urinary methylmalonic acid or performing the Schilling's test aids in the diagnosis.

HEREDITARY OPTIC NEUROPATHIES

The designation of hereditary optic neuropathy describes many different genetic abnormalities that are transmitted in a variety of inheritance patterns. Autosomal recessive inheritance is associated with severe visual loss from infancy. Dominant inheritance patterns characteristically have milder disease with delayed onset, which may be difficult to distinguish from toxic/nutritional neuropathies. Optic atrophy may also occur with heritable neurodegenerative disorders associated with spinocerebellar disorders, deafness, ataxia, and motor and sensory neuropathies.

KJER'S DOMINANT OPTIC NEUROPATHY

This dominantly inherited disorder causes a bilateral, symmetric, slowly progressive central or cecocentral visual field loss (Fig. 4-19). Visual abnormalities usually begin in childhood, between the ages of 4 to 10, and may progress into the early teens. By the midteens, the vision stabilizes, typically with a visual acuity around 20/100. Classically, the Farnsworth-Munsell 100 hue test demonstrates a tritanopic axis. The inheritance pattern may not be obvious in the family history, as incomplete penetrance is common. Although many patients are aware that their vision has been subnormal their entire life, some patients are not symptomatic until adulthood. The family history should be explored in detail by constructing a family tree if possible, identifying known or potentially affected individuals. The optic discs typically display temporal pallor but may appear relatively normal. Nerve fiber layer defects in the papillomacular bundle may be evident.

LEBER'S HEREDITARY OPTIC NEUROPATHY

Leber's hereditary optic neuropathy (LHON) is a heritable disorder that tends to affect males in their second and third decades of life (Fig. 4-20). This genetic defect is peculiar because it manifests as acute visual loss in one eye,

typically followed by a similar event in the fellow eye within weeks. The precipitating factors are unknown, but in some cases, alcohol or tobacco abuse or a nutritional deficiency is suspected. The visual field defect is usually a central or cecocentral scotoma that may continue to worsen over several months. The effect on the visual acuity ranges from mild to profound. Some patients have an inexplicable spontaneous recovery years later.

The optic disc may be mildly hyperemic with swelling of the peripapillary nerve fiber layer or may appear normal. Peripapillary telangiectatic dilation of small retinal capillaries is the classic finding, but it is difficult to identify unless specifically sought. These vessels do not leak on intravenous fluorescein angiography and may be best seen in an unaffected eye. Disc pallor develops shortly after visual loss, with loss of the peripapillary vascular changes.

The genetic abnormality responsible for LHON is in themitochondrial DNA. Although most genetic information is contained in the nuclear DNA (chromosomes), small strands of circular DNA in the mitochondria code for certain crucial components involved in energy metabolism. The list of disorders thought to be related to abnormalities in mitochondrial DNA is growing. At least three genetic defects in mitochondrial DNA have been conclusively linked to LHON. These disorders are designated by the position of the point mutations in well-conserved regions of the mitochondrial DNA sequence: 11778 (also called the "Wallace mutation"), 14484, and 3460.

The inheritance pattern of mitochondrial genetic disorders is unique. At conception, the mitochondrial DNA in the sperm is excluded from the fertilized egg. The offspring receives mitochondrial DNA exclusively from the mother. Thus the genetic defect in LHON is passed from a female carrier to both male and female offspring. All daughters are carriers and can occasionally manifest the disease. All sons have the genetic defect and frequently manifest the disease but do not pass the defect to their children. The disorder is therefore exclusively maternally inherited but manifests mostly in male offspring.

Many patients with LHON are initially thought to have optic neuritis because the clinical presentation may be similar. However, pain with eye movement (a common finding in optic neuritis) is absent in LHON. The diagnosis can be made by identifying the specific genetic mutations from a blood specimen, but this molecular genetic evaluation generally takes weeks to perform. Unless the case is absolutely classic with an established family history, most patients have neuroimaging and laboratory studies to evaluate for other potential causes of visual loss. Once the mutation has been identified, genetic counseling for the patient and family is indicated. Because of a potential association with cardiac conduction abnormalities, an electrocardiogram should be obtained in patients with LHON. Also, patients at risk for LHON should be advised not to use tobacco and to limit alcohol intake, as environmental factors may play a

role in triggering visual loss. No proven effective treatment is available, but many clinicians recommend dietary supplementation with vitamins and co-enzymes.

TRAUMATIC OPTIC NEUROPATHY

Trauma to the optic nerve can be produced directly or indirectly. Examples of direct trauma include the impact of a BB shot on the intraorbital nerve, injury from a needle during retrobulbar injection, or impalement of the nerve by a bone fragment from a fracture of the optic canal (Fig. 4-21).Indirect trauma frequently occurs with blunt trauma involving the orbital rim or forehead, with the conical shape of the bony orbit transmitting forces to the apex and optic canal, causing a contusion of the optic nerve even in the absence of a fracture involving the optic canal (Fig. 4-22).

Symptoms

Visual loss is often immediate at the time of trauma and does not change over time. An important subgroup of patients may have a "lucid interval," followed hours or days later by a precipitous drop in vision caused by expanding optic nerve edema or hemorrhage.

Signs

Traumatic optic neuropathy may initially present with a normal-appearing optic disc. Optic disc pallor, and occasionally cupping (in young patients), becomes evident over several weeks or months.

Optic nerve trauma only occasionally appears as an isolated finding. The potential for coincident trauma involving the adnexa, orbit, and globe, as well as head and body trauma, must be actively addressed.

Causes

The mechanism of direct trauma is no mystery. Axons and their support tissue are damaged by shearing, compression, contusion, or accompanying interruption of their vascular supply. Indirect trauma can be just as severe, with contusion of the optic nerve from shock waves transmitted by the orbital bones to the orbital apex and optic canal. Additional damage to the optic nerve may be caused by optic nerve edema within the confines of the bony optic canal. A compartment syndrome may develop with ischemia to the optic nerve, causing even further edema and compression. This cycle of edema and ischemia is most likely the mechanism in patients whose visual loss is delayed for hours or days following trauma.

Differential diagnosis

In most cases, the presentation of traumatic optic neuropathy is self-evident, with history, examination, and other manifestations of trauma leaving little doubt. Occasionally, patients may present with a pale optic nerve and an uncertain history; these patients require neuroimaging. Progressive visual loss with optic nerve pallor is not consistent with traumatic optic neuropathy and suggests a compressive optic neuropathy.

Evaluation

Because a search for skull and orbital fractures is indicated in most cases, a CT scan of the brain and orbits is more appropriate than MRI as an initial study. True coronal slices provide the most information, but the flexion or extension of the neck may be impractical and require clearance of the cervical vertebrae first. Evaluation of optic nerve injury is also complicated by the fact that these patients frequently have "higher priority" traumatic injuries that may be life-threatening.

Treatment

Debate regarding the treatment of traumatic optic neuropathy is ongoing. Theoretically, the use of high dose steroids in the acute setting seems reasonable, but to date there is no convincing evidence that this treatment is effective. Surgical decompression of the optic canal, either neurosurgically or with an ethmoid sinus approach, has also been offered as a treatment of traumatic optic neuropathy. The efficacy of this procedure is unproven, and the potential for surgical morbidity must be considered. Stable, metallic foreign bodies in the orbit may not require removal. Surgery to relieve fracture fragments compressing or impinging on the optic nerve is controversial.

Clinical course

Sequential evaluation of visual function is crucial in the immediate posttrauma period. After this period, visual function is expected to be unchanging, and documenting this visual stability with perimetry several months after the event is useful.

GLAUCOMA

Primary open-angle glaucoma is the most common disorder causing an optic neuropathy (Fig. 4-23). Because an entire volume in this series is devoted to this disorder, this discussion is limited to aspects of interest to neuro-ophthalmology.

Patients with primary open-angle glaucoma typically have elevated intraocular pressures, gradual enlargement of the optic cup, and peripheral visual field defects. However, the intraocular pressure does not always correlate with progressive visual field loss, and visual loss may occur even in patients with normal pressures. Atrophy of axons causes enlargement of the optic cup, predominantly with loss of neuroretinal tissue at the superior and inferior aspects of the cup, resulting in vertical elongation of the cup that "notches" the neuroretinal rim. Glaucoma does not typically cause pallor of the neuroretinal rim. Patients with cupping and rim pallor likely have another underlying diagnosis and require further investigation.

Visual field loss from glaucoma usually correlates relatively well with the degree and location of optic disc cupping. The pattern of visual field loss is remarkably similar to chronic optic disc edema, with preservation of central vision until late in its course. New visual field changes may be heralded by characteristic flame-shaped hemorrhages at the disc margin.

Occasionally, other optic neuropathies are misdiagnosed as glaucoma. Visual field defects that do not correlate with optic disc cupping, the presence of pallor of the neuroretinal rim, and early loss of central vision suggest a diagnosis other than glaucoma. Patients with "normal pressure" (or low tension) glaucoma may require consideration of other diagnostic possibilities, such as a compressive optic neuropathy or syphilitic optic atrophy.

ANOMALOUS OPTIC DISCS

OPTIC DISC DRUSEN

Optic disc drusen are mineralized hyalinelike crystals of unknown origin embedded in the substance of the prelaminar optic nerve head (Fig. 4-24). Optic disc drusen are present in about 1% of Caucasians and are frequently bilateral (75%). Optic disc drusen can be inherited as an autosomal-dominant trait with incomplete penetrance.

Microscopically, drusen appear as concentric layers of hyalinoid material, with positive staining for amino acids, acid mucopolysaccharide, calcium, and hemosiderin, but not amyloid.

Symptoms

Optic disc drusen are frequently an incidental discovery during an eye examination. Occasionally, patients present complaining of peripheral visual loss. Rarely, patients may experience a relentless, progressive, stepwise decline in peripheral vision. Transient visual obscurations, similar to those seen in papilledema, may occur with disc drusen.

Signs

In young patients, optic disc drusen may be buried within the disc and not visible with ophthalmoscopy (Fig. 4-25). These discs are elevated, often with a "lumpy-bumpy" contour, and may simulate optic disc edema (pseudopapilledema) (see Box 4-2). Over time, the drusen "emerge," perhaps because of atrophy of the overlying nerve fibers. Disc drusen in older patients are usually evident with the ophthalmoscope, appearing as glistening, yellowish, "rock candy" crystals poking through the nerve fibers of the disc. Peripapillary choroidal neovascular membranes can occur in association with disc drusen. Optic disc drusen may be associated with retinitis pigmentosa and angioid streaks.

Optic-disc-related visual field defects, with corresponding loss of the retinal nerve fiber layer, may be present. Curiously, central visual acuity is almost never affected. Profound peripheral visual field loss with central sparing from optic disc drusen is a potential cause of peripheral constriction with preservation of central vision (see Table 3-3).

Causes

The precise mechanism of visual loss in patients with optic disc drusen is unknown, but it likely relates to the typical crowded configuration of these patients' optic discs. Axonal atrophy may occur secondary to compression of optic nerve axons, but the position and extent of disc drusen do not correlate well with the visual field defects. Some patients present with an acute event, demonstrating true optic disc edema in addition to the presence of disc drusen, implicating a drusen-related AION.

Differential diagnosis and evaluation

Buried disc drusen may give the appearance of optic disc edema ("pseudopapilledema"). On the other hand, the tiny, glistening edema residues often accompany chronic optic disc edema and should not be mistaken for drusen (see Box 4-2). Disc drusen not evident with the ophthalmoscope are best identified with orbital ultrasound, appearing as focal, highly echoic densities (Fig. 4-24, C-D). The calcific component of the drusen also makes them highly visible on computerized tomography images that include the optic nerve head (Fig. 4-25, B). Drusen exhibit autofluorescence, demonstrated with the standard barrier and exciter filters of the fluorescein angiogram camera, without the need of fluorescein. This property is more interesting than useful, however, because the drusen that can be seen with this method are usually evident with the ophthalmoscope (Fig. 4-24, B).

Systemic hypotension may be a risk factor for visual loss. Patients with stepwise visual field loss and optic disc drusen should be evaluated for orthostatic hypotension.

The discovery of optic disc drusen in a patient with elevated discs may save the patient from an extensive evaluation for optic disc edema. However, the presence of drusen does not preclude other diseases; for example, patients with optic disc drusen can also have true papilledema. The clinician should actively seek evidence of other potential disorders and investigate any clues not consistent with disc drusen. Progressive visual loss requires an extensive evaluation including neuroimaging to look for possible optic nerve compression.

Treatment

As previously discussed, the mechanisms of visual loss from optic disc drusen are not entirely understood. The presence of systemic orthostatic hypotension in some patients with progressive visual field loss suggests that vascular hypoperfusion may play a role. Rarely, a patient may need medical treatment for hypotension. Some clinicians suggest topical agents to lower the intraocular pressure in an effort to improve the ocular perfusion gradient.

Other Optic Disc Anomalies

The term anomalous optic disc implies a congenital rather than acquired abnormal optic disc appearance. Disc anomalies may be minor and may not affect optic nerve function (crowded, elevated, or tilted discs; or myelinated retina nerve fibers), or may represent significant maldevelopment of the visual pathway (hypoplasia, aplasia, or coloboma) (Fig. 4-26).

Crowded optic discs

Small discs that are "cupless" may be at risk for AION (see previous discussion) (Fig. 4-26, A).

Elevated discs without drusen

Some anomalous optic discs that appear elevated may not harbor disc drusen (Fig. 4-26, B). This optic disc appearance typically occurs in young patients and is usually bilateral, mimicking papilledema. Concern is heightened when drusen are not clinically identified. Some of these optic discs may eventually develop drusen. Box 4-2 lists some characteristics to help distinguish true from pseudopapilledema.

Tilted optic discs

This anomaly results from an oblique insertion of the optic nerve on the globe and is a frequent finding in axial myopia (Fig. 4-26,C). The nasal edge of the disc is elevated, and the temporal edge and adjacent retina are depressed relative to the normal plane of the peripapillary retina. These discs appear vertically elongated, with a crescent-shaped white area temporally where the retinal pigment epithelium stops short of the disc edge. The depression of retina

temporal to the disc may cause a scotoma, occasionally simulating the bitemporal visual field defects of chiasmal disorders (see Box 3-2).

Myelinated retinal nerve fibers

Myelination of the anterior visual pathway begins at the lateral geniculate body during gestation, proceeding anteriorly and reaching the lamina cribrosa of the optic nerve head at about term. In less than 1% of the population, myelination abnormally proceeds into the eye and retinal nerve fiber layer for a variable extent. This creates white, opaque patches in the nerve fiber layer of the retina, usually adjacent to the optic disc, that may be confused with optic disc swelling. Myelinated retinal nerve fibers are not associated with disease, and generally do not cause symptomatic visual loss.

Hypoplasia

Optic disc hypoplasia represents incomplete development of the optic disc, characterized by a small optic disc with a larger concentric variably pigmented ring ("double-ring sign") (Fig. 4-26,E). Visual function may be poor or relatively good. Disc hypoplasia may occur in one or both eyes and has been reported in children born to diabetic mothers or mothers who have been exposed to alcohol, LSD (lysergic acid diethylamide), quinine, or antiepileptic drugs during pregnancy. Disc hypoplasia is one component of septo-optic dysplasia (de Morsier syndrome), which also includes absence of the septum pellucidum and neuroendocrine axis dysfunction (often resulting in short stature). A hypoplastic appearance of the optic disc can also be caused by arrested development resulting from craniopharyngiomas or glioma. Neuroimaging and determination of endocrine function may be required in the evaluation of optic disc hypoplasia in children, especially in bilateral cases.

Aplasia

A complete failure of optic nerve development is rare and is usually associated with lethal congenital neural abnormalities.

Coloboma

Incomplete closure of the fetal fissure in ocular development can initiate a broad spectrum of optic disc and chorioretinal development abnormalities, termed colobomas. One extreme coloboma is the "morning glory syndrome," consisting of marked excavation of an enlarged disc with embryonic glial remnants extending from the disc in the shape of a flower. Optic nerve pits represent a mild abnormality in the spectrum of developmental disc anomalies, but

associated macular subretinal fluid can cause a profound effect on vision (Fig. 4-26, F). Optic disc and chorioretinal colobomas are typically located inferior and temporal to the disc, along the site of the fetal fissure (Fig. 4-27). Visual dysfunction generally parallels the degree of optic disc malformation. Developmental optic disc abnormalities may be associated with forebrain abnormalities, particularly basal encephaloceles.

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4-1

The vascular supply to the anterior optic nerve. Observe that the prelaminar and laminar portions of the optic nerve head do not receive their blood supply from the central retinal artery but depend on the short posterior ciliary arteries.

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4-2

Optic disc edema. Massive optic disc edema is present in this patient with intracranial hypertension and systemic hypertension. The optic nerve is elevated and enlarged. Hemorrhage is present in the nerve fiber layer (flame-shaped hemorrhages) and within the retina (dot/blot hemorrhages). The swollen nerve elevates and laterally displaces the choroid and retina, creating concentric retinal folds called Paton's lines. (See color plate.)

4-3

Common causes of optic disc swelling. Although optic disc swelling has many causes, a thorough history and examination helps to narrow the possibilities. The more common diagnostic possibilities can often be distinguished by whether one or both optic discs are involved, the age of the patient, and the degree of visual loss.

4-4

Nonarteritic anterior ischemic optic neuropathy. A 62-year-old male awoke with painless visual loss in his left eye. A, A dense inferior altitudinal visual field defect was present in the left eye; the visual field in the right eye was normal. B, The right disc was normal, but note the absence of a central cup. The left optic disc was swollen. The optic disc edema primarily involves the upper half of the optic disc, corresponding to the inferior visual field defect. (See color plate.) C, After six weeks, the upper pole of the left optic disc was less swollen but pale. Paradoxically the lower pole appeared more swollen, with telangiectatic vessels that may represent "luxury perfusion" to the remaining normal nerve. (See color plate.) D, After six months, the upper portion of the left optic disc was now pale, and the lower half remained pink. (See color plate.) E, Clinical course of visual loss. The visual loss in this disorder is sudden, but may decline stepwise over several days. Some patients may have slight improvement in their central vision with time, but the visual field defect is generally permanent.;E>

4-5

Arteritic anterior ischemic optic neuropathy (giant cell arteritis). A 74-year-old female described brief episodes of visual loss in her right eye for several days, followed by a "skim" over the right eye two days before her evaluation, and awoke the next day with "no vision" in the right eye. She reported general malaise and tenderness over the temples for two weeks. The examination showed only light perception vision in the right eye, with pale optic disc swelling. Although the ESR was relatively normal for her age (41 mm/hr), giant cell arteritis was suspected on the basis of the history and examination. The patient was admitted for high-dose intravenous steroids, and a temporal artery biopsy confirmed the diagnosis of giant cell arteritis. A, Pale optic disc edema was present in the right eye. (See color plate.) B, Temporal artery exposed at biopsy. The artery appeared large and pale. (See color plate.)C, Temporal artery cross section, H&E stain, 100×. The lumen is obliterated by massive thickening of the arterial wall. Fracture of the internal elastic lamina is seen (arrow). (See color plate.) D, A multinucleated giant cell is seen at higher magnification (circle). (See color plate.)

(Photomicrographs (C and D) courtesy of Constance Stanton, M.D.);D>

4-6

Intravenous fluorescein angiogram in arteritic anterior ischemic optic neuropathy. The early phase of an intravenous fluorescein angiogram shows a large nonfilling segment of the choroid in a patient with anterior ischemic optic neuropathy from giant cell arteritis(arrows).

4-7

Diabetic papillitis. A 37-year-old insulin-dependent diabetic patient described a sudden change in the vision of his left eye. A, The right optic disc is relatively normal, but diabetic retinopathy is evident in both eyes. The left optic disc is diffusely edematous with disc and peripapillary hemorrhages. B, Automated perimetry of left eye showed only a small inferior nasal step, far less than expected from the degree of optic disc edema. The visual acuity was 20/80. The visual field in the right eye was normal.C, Three months later, the optic disc edema in the left eye was nearly resolved, with mild pallor remaining. The central acuity improved to 20/40, but visual field defect remained unchanged.

4-8

Papillophlebitis. A 35-year-old male described a "smudge" in the vision of his right eye. The best corrected visual acuity was 20/40 in the right eye and 20/20 in the left eye. A, Optic disc edema with peripapillary hemorrhages, cotton wool spots, and venous engorgement was present in the right eye. Unlike a central retinal vein occlusion, no hemorrhages were present in the retinal periphery. The fundus abnormalities and symptoms gradually cleared over four months.B, Automated perimetry of the right eye showed minimal diffuse depression with a mean deviation of −4.43. The left eye had a normal visual field (mean deviation of −2.00 decibels).

4-9

Optic neuritis and multiple sclerosis. A 32-year-old female had pain with eye movement and decreased vision in her right eye. A, The initial visual field of the right eye showed dense visual field loss in three quadrants. The visual acuity was 20/80 and a 1.2 log unit RAPD was present. The left eye was normal. B, Mild diffuse disc edema was present in the right eye; the left optic disc was normal. (See color plate.) C, An MRI of the orbits (T1-weighted image with contrast, coronal view) revealed enhancement of the right optic nerve (arrow). D, The MRI of the brain (T2-weighted image, axial view) revealed periventricular white matter plaques characteristic of multiple sclerosis(arrows). Additional T2 signal abnormalities were seen in the right pons (not shown). As suggested by the ONTT, three days of high-dose intravenous methylprednisolone were administered.E, Within three weeks of onset, the visual field demonstrated dramatic improvement. A shallow central scotoma remained, with a visual acuity of 20/40. Eventually, the visual field and acuity normalized, but a small RAPD was still present two years later.F, Time course of visual loss.

Optic neuritis typically causes a decline in vision over several days to a week, followed by a slow but steady recovery over several months. Patients often achieve near-normal visual acuities and visual fields, but they may indefinitely note a subjective difference in the brightness or quality of vision in the affected eye.

4-10

Idiopathic intracranial hypertension. A 40-year-old female presented with a history of headache and transient visual obscurations in her left eye for eight months and blurred vision in her left eye for two months. A, Bilateral optic disc edema at presentation. Paton's lines can be seen at the temporal edge of the left disc. (See color plate.) B, The visual field in the left eye showed a dense inferior altitudinal visual field defect. In the right eye, an inferior nasal step is identified. The presence of visual field defects suggested that the papilledema was chronic, rather than acute. An MRI with contrast of the brain was normal, and a lumbar puncture revealed an opening pressure of 368 mm of water with normal CSF studies. Acetazolamide 500 mg BID and an effective weight loss program was instituted, with resolution of optic disc edema in about six months. C, These optic disc photographs from one year after presentation show resolution of the optic disc edema, with mild pallor remaining. (See color plate.)D, The visual field defects also improved, but a dense inferior nasal step remains in the left eye.

4-11

Intracranial hypertension from dural sinus thrombosis. A 32-year-old female complained of severe headache, increasing in intensity over three weeks. A, Optic disc edema was present bilaterally, more prominent in the left eye. B, The visual fields were relatively normal, with only mild enlargement of the blind spots.C, MRI of the brain (T2-weighted image, axial view) revealed bright signal (rather than the normal flow void) in the right transverse (arrows) and sigmoid dural sinuses, indicative of thrombus. D, Magnetic resonance angiography (MRA) demonstrated absence of flow in the right transverse(arrows) and sigmoid sinus. The patient was admitted to the neurology service and treated with both acetazolamide and anticoagulants. Although the optic disc edema resolved within two months, headache has continued to be a chronic problem.

4-12

Bilateral optic disc edema from malignant hypertension. A 9-year-old male was referred for blurred vision and "papilledema." Bilateral hyperemic optic disc edema was present, with retinal hemorrhages, cotton-wool spots, retinal arteriolar narrowing, and macular edema residues. The blood pressure was 200/105. The patient was admitted to

pediatric ICU for management of malignant hypertension. Neuroimaging was normal. Further evaluation confirmed renovascular hypertension.

4-13

Optic nerve sheath meningioma. A 51-year-old female had left optic disc edema for three years, with normal CT scans. A subjective decline in vision led to further investigation, with the diagnosis of an optic nerve sheath meningioma based on MRI studies. A, Chronic, diffuse edema of the left optic disc is present. B, Automated perimetry of the left eye at the time of diagnosis shows an inferior nasal step. The visual acuity was 20/20. C, Four years later, the nasal step has enlarged, and is nearly an altitudinal defect. The visual acuity at this time is 20/40. D, MRI of the orbit (with enhancement, coronal plane). The meningioma is seen as an enhancing mass surrounding the compressed, nonenhancing optic nerve(arrow). E, MRI (axial plane) reveals that the meningioma is present in the orbit and extends through the optic foramen intracranially but does not include the chiasm(arrows). F, Clinical course. A steady decline of vision is the general rule with compressive lesions.

B

4-14

Optic nerve glioma and neurofibromatosis. A 6-year-old female was seen by her ophthalmologist with a "right eye turning in." A diagnosis of neurofibromatosis (NF-1) had recently been made on the basis of cafe-au-lait spots and a known family history of NF-1. A right optic nerve glioma was discovered. The patient's visual acuity was 20/80 at the time of diagnosis and has remained stable for more than three years without treatment. A, Diffuse elevation and edema of the right optic disc is evident. The left disc is normal. B, MRI (T1 axial view) reveals massive enlargement of the right optic nerve (arrow), causing mild proptosis.;A>;B>

4-15

Glioma of the anterior visual pathway in an adult. A 36-year-old male with a diagnosis of glioblastoma multiforme in the right parietal region had received both conventional and gamma knife radiation therapy. A complete left homonymous hemianopic visual field defect was present. The patient presented with visual loss in the right eye, decreasing to NLP over two weeks. Marked optic disc elevation and retinal venous stasis is present in the right eye; the left optic disc is normal (pictured). Repeat neuroimaging demonstrated anterior extension of the malignant glioma into the right optic nerve.

4-16

Acute leukemic optic nerve infiltration. A 10-year-old male with acute lymphocytic leukemia presented with bilateral blurred vision. Both optic nerves were enlarged and elevated, with hemorrhages and cotton wool spots present, suggesting acute leukemic optic nerve infiltration(pictured). Urgent radiation of the optic nerves resulted in partial recovery of visual loss.

4-17

Neuroretinitis from cat-scratch disease. A 10-year-old female complained of blurred vision in her left eye that began two weeks after a self-limited, four-day febrile illness. She frequently played with the family's kitten. Enzyme immunoassay for Bartonella henselae was positive. A, The left fundus showed optic disc edema and edema residues forming a macular star. Focal disc elevation suggesting a granuloma can be seen on the temporal disc. (See color plate.) B, Goldmann perimetry initially showed a dense cecocentral scotoma. Visual acuity was CF 2`. The patient was treated with oral doxycycline hyclate, 100 mg daily for 10 days. In one month, the acuity improved to 20/200, and was 20/20 within four months, with normalization of the visual field defect. C, Peripheral fundus. Deep chorioretinal white spots are often present in both eyes even when the neuroretinitis is confined to one eye, as demonstrated in another patient with cat-scratch neuroretinitis.

4-18

Toxic/nutritional optic neuropathy. A 59-year-old male reported the gradual onset of poor vision in both eyes. He admitted drinking "too much" alcohol but believed he ate a well-balanced diet. Visual acuity was 20/80 in each eye, with a normal slit-lamp and ophthalmoscopic examination. A, The visual field on presentation showed bilateral cecocentral scotomas, best appreciated by looking at the total deviation plots. A nutritional optic neuropathy was suspected, and the patient was started on a multivitamin, as well as folate 1 mg daily, and referred to his general medical doctor to address his diet and probable alcoholism. B, Four weeks later, the automated visual field had improved significantly, with improvement of visual acuity to 20/30 in each eye. The patient's visual acuity and visual fields were normal when tested after an additional six weeks. The patient said he was compliant with his vitamin therapy, but admitted his alcohol was only minimally reduced.

4-19

Kjer's dominant optic atrophy. A 43-year-old female has had subnormal vision her entire life. With a known family history of visual loss, she also brought her 18-year-old asymptomatic daughter for evaluation.A, The mother's optic discs show diffuse pallor, with more striking pallor temporally. B, Bilateral cecocentral scotomas were present

with Goldmann perimetry. The visual acuity was 20/200 in both eyes. C, The daughter's optic discs showed bilateral temporal pallor. (See color plate.) D, The daughter's automated perimetry showed bilateral shallow central scotomas. The visual acuity was 20/50 in each eye.Continued

4-20

Leber's hereditary optic neuropathy (LHON). A 19-year-old male described the sudden onset of blurred vision in his right eye, which continued to progressively worsen. Two months after the onset of visual loss in his right eye, the vision in the left eye declined rapidly. LHON was confirmed with the identification of a mitochondrial DNA mutation at position 3460. A, Optic discs, two months after onset of visual loss in the right eye, just before symptoms began in the left eye. Mild temporal pallor of the right optic disc is present. The left optic disc is hyperemic, with subtle peripapillary telangiectatic vessels present. (See color plate.) B, Left optic disc, three months after presentation, after both eyes are affected. The disc hyperemia and telangiectasia have resolved, with mild temporal pallor now present. C, Goldmann visual fields demonstrate bilateral cecocentral scotomas.

4-21

Direct optic nerve trauma. A 12-year-old male was injured when a BB struck his right orbit. The entry wound was in the temporal conjunctiva, missing the globe. The visual acuity was 20/50 and a cecocentral scotoma was present. The CT scan (axial image) shows the BB adjacent to the right optic nerve. Acutely, the right optic disc appeared normal, but it turned pale over the following four weeks.

4-22

Indirect traumatic optic neuropathy. Forces generated from a blow to the orbital rim can be transmitted to the optic canal, contusing the optic nerve even in the absence of fracture.

4-23

Primary open-angle glaucoma. A 44-year-old male has primary open-angle glaucoma. A, The cup of the right optic disc is enlarged, and the neuroretinal rim has an inferior "notch." Note that the neuroretinal rim is thin but not pale. B, Automated perimetry shows a dense superior altitudinal visual field defect in the right eye, corresponding to the notching of the inferior neuroretinal rim.

4-24

Optic disc drusen and visual field loss. A 62-year-old male reported that vision in his right eye has been better than in his left eye for many years. A, The right disc appears normal; optic disc drusen are evident on the left. B, By

using the barrier filters for fluorescein angiography without fluorescein dye injection, autofluorescence can be detected. Faint autofluorescence can be seen in the inferior portion of the right disc, suggesting buried disc drusen. Diffuse autofluorescence of the left optic disc is evident. C, B-mode ultrasound of the right eye shows the highly echoic buried disc drusen (arrow), even though it is not seen with the ophthalmoscope. D, B-mode ultrasound of the left eye shows the bright echo signals from florid optic disc drusen (arrow). E, In the left eye, dense peripheral visual field loss is evident, with preservation of the central acuity (20/25). The right eye has a normal visual field and acuity.

4-25

Pseudopapilledema from buried optic disc drusen. A 16-year-old female was noted to have elevated optic discs and headaches. Visual acuity and visual fields were normal. A CT scan of the brain was reportedly normal. B-mode ultrasound of the optic discs revealed buried optic disc drusen (as in Fig. 4-24). A, The optic discs are elevated with a "lumpy-bumpy" contour. B, A review of the patient's CT scan (axial view, bone windows) also revealed the radiodense drusen.;A>;B>

4-26

Anomalous optic discs. A, Small cupless optic discs.B, Anomalously elevated optic discs without clear evidence of drusen. C, Tilted optic discs with an inferior temporal conus in a patient with high myopia. D, Myelinated nerve fiber layer simulating optic disc edema. E, Optic disc hypoplasia with a "double-ring" sign. F, Optic nerve head pit (arrow).

4-27

Ocular coloboma. A, Bilateral inferonasal iris defects suggest that this patient had incomplete closure of the fetal tissue during embryonic development. B, This "fundusmap" of the patient's right eye was digitally created from many individual 30-degree photographs. A large coloboma involves the retina and optic disc (seen at the superior edge). The left eye was nearly identical.

(B, courtesy of R. Hackell.);B>

4-1

Findings and recommendations of the ONTT

Findings	Recommendations
Patients who received oral steroids alone had a significantly higher rate of recurrence of optic neuritis than the other two treatment groups.	Do not treat patients with optic neuritis with oral prednisone alone.

Patients with white matter plaques on an infused MRI were more likely to have neurologic events suggestive of MS following optic neuritis than were those with a normal MRI. The risk of developing MS was reduced in those patients with MRI findings who received intravenous steroids, but only for about two years; by three years no lasting affect was evident. An MRI with contrast is helpful in predicting the probability of MS, and should be done if the diagnosis is uncertain. Those patients with white matter plaques should be considered for intravenous methylprednisolone treatment to reduce the short-term risk of developing other neurologic symptoms.

Since there is no proven long-term advantage, prescribing

no treatment is also a reasonable approach.

Patients treated with intravenous steroids improved more quickly than untreated patients, but all patients improved to the same degree within six months to a year. Although intravenous steroids offer no long-term advantage for visual recovery, a more rapid recovery may be beneficial in patients whose only or better eye is affected.

4-2

Causes of intracranial hypertension related to impediments of CSF flow and absorption

Segment of CSF pathway affected Cause of increased intracranial pressure Mechanism

CSF is produced in the choroid plexus of the lateral and fourth ventricles, Choroid plexus papillomas produce

excess CSF CSF overproduction is only rarely a cause of increased intracranial pressure.

flows through the ventricular system . . . Aqueductal stenosis and other causes

of noncommunicating hydrocephalus Expanding ventricles from obstruction of outflow

into the subarachnoid space, and

is absorbed by the arachnoid

granulations . . . Meningitis (bacterial, viral, parasitic), carcinomatous meningitis. See other causes in Box 4-8. Injury to the arachnoid villi with inadequate absorption, or toxic effects

into the adjacent superior sagittal venous sinus. Venous blood flows though the dural venous sinuses, draining into . . . Dural sinus thrombosis, dural AVM Elevation of venous sinus pressure retards CSF egress.

the jugular system in the neck, Radical neck dissection (with sacrifice

of jugular system), superior vena cava syndromes Venous pressure in the cranial venous sinuses can be elevated by any impediment to distal venous blood flow.

superior vena cava, and right heart. Right heart failure, congestive heart

failure, cor pulmonale

4-1

Causes of Optic Disc Elevation*

Papilledema (elevated intracranial pressure)

Optic neuritis (demyelinating)

Anterior ischemic optic neuropathy

nonarteritic

giant cell arteritis

diabetic papillitis

Compression

Graves' disease

meningioma

orbital masses

Infiltration (inflammatory and neoplastic)

sarcoidosis

lymphoproliferative disorders

glioma

Infection

syphilis

cat-scratch disease

toxoplasmosis

Leber's hereditary optic neuropathy (LHON)

Venous congestion

retinal vein occlusion

papillophlebitis

dural-cavernous fistula

Other ocular disorders

uveitis

hypotony

cystoid macular edema

Systemic

malignant hypertension

severe anemia

hypoxemia

cyanotic heart disease

uremia

Anomalous discs

optic disc drusen

gliosis

Optic disc tumors

hemangiomas

melanocytoma

metastasis

Other

trauma

*Both "true" and "pseudo" optic disc swelling.

4-2

Distinguishing True Optic Disc Edema from Anomalous Optic Discs (Pseudopapilledema)

Common features of anomalous optic discs

Often "cupless" with small diameter

Venous pulsations often present, but may be absent

Increased number of central retinal vessels arising from the apex of the disc

Abnormally increased branching of central retinal vessels on the disc

Scalloped border or lumpy contour when buried drusen are present

Visible optic disc drusen may be present

Common features of "true" optic disc edema

Central cup usually preserved unless edema is extreme

Increased "capillarity" of optic disc

Concentric peripapillary chorioretinal folds (Paton's lines)

Radial choroidal folds

Leakage on intravenous fluorescein angiography

Glistening tiny "pseudodrusen" edema residues on disc

Associated cotton wool spots

Associated retinal hemorrhage (can occasionally occur with anomalous discs)

4-3

Hematalogic Abnormalities That Can Cause Vascular Occlusions

Hypercoaguable states

Protein C deficiency

Protein S deficiency

Antithrombin III deficiency

Antiphospholipid antibodies

Lupus anticoagulant

Anticardiolipin antibodies

Factor V Leiden mutation (activated protein C

resistance)

Erythrocyte disorders

Polycythemia

Sickle-cell disease and others

4-4

Acquired Causes of Profound Visual Loss with a Relatively Unremarkable Fundus Examination

Retrobulbar optic neuritis: Young adults with monocular visual loss and RAPD.

Compressive optic neuropathy: Optic disc becomes pale eventually but may look normal at first.

Giant cell arteritis (posterior ischemic optic neurop-

athy): patients more than 55 years old with acute visual loss and symptoms of systemic vasculitis.

Acute traumatic optic neuropathy: Pallor may take weeks to develop following injury.

Unilateral retrochiasmal lesions: Homonymous visual field defects do not affect visual acuity.

Bilateral occipital lobe infarction: Bilateral, symmetric visual loss with relatively equal visual acuities and congruous field loss.

Retrobulbar inflammatory or infiltrative disorders: Neurosarcoidosis, orbital inflammatory pseudo-tumor may not initially cause pallor or edema.

Retinal artery occlusion: After the acute retinal edema has resolved, retinal findings may be subtle.

Paraneoplastic retinopathy: Bilateral, symmetric, slowly progressive visual loss.

Toxic and nutritional optic neuropathies (or maculopathies): Bilateral, progressive loss of central vision.

4-5

Ischemic Consequences of Giant Cell Arteritis

Ophthalmic

Anterior ischemic optic neuropathy

Posterior ischemic optic neuropathy

Central retinal artery occlusion

Ocular ischemic syndrome

Ischemic cranial neuropathies

Ischemia of extraocular ocular muscles

Systemic

Common

Jaw and tongue claudication

Scalp ischemia

Uncommon

Myocardial infarction

Mesenteric insufficiency

Stroke

4-6

Steroid "Dependent" Disorders Affecting Vision

NEOPLASTIC

Optic nerve glioma

Optic nerve sheath meningioma

Chromophobe adenoma

Craniopharyngioma

Medulloblastoma

Lymphoproliferative optic nerve infiltration/

compression

Meningeal carcinomatosis

PARANEOPLASTIC

Retinopathy

Optic neuropathy

INFLAMMATORY

Sarcoidosis

Orbital inflammatory pseudotumor

Vasculitis (giant cell arteritis)

OTHER

Autoimmune optic neuropathy

4-7

Muliple sclerosis

Multiple sclerosis (MS) is an autoimmune disorder with focal, patchy destruction of white matter in the brain, spinal cord, and optic nerves of unknown cause. The disease is more common in females (2 to

1 female-to-male ratio), and is most common in the young adult age group (25 to 40 years). The risk of developing MS increases 20-fold in first-degree relatives of patients with multiple sclerosis. The incidence of MS rises with increasing distance from the equator.

Patients who move after the age of 15 carry the risk

of their original locale with them. Patients who move before the age of 15 seem to acquire the risk of a new location.

The disease is a chronic relapsing, remitting

disorder that commonly causes visual symptoms,

including optic neuritis and diplopia. Systemic findings include extremity weakness, cerebellar dysfunction (causing vertigo and ataxia), paresthesias of the face and body, and urinary retention or incontinence.

Many patients have episodes of reversible neurologic dysfunction that may be separated by many months

or years. Approximately one third of patients with

MS have no physical disability or decreased life expectancy, but 10% of patients have a relentlessly progressive form. Patients who are older at the time of

diagnosis have a poorer prognosis than do younger

patients.

A diagnosis of multiple sclerosis is made by identifying neurologic symptoms that are separated in time and space (affecting different areas of the central nervous system). Although MRI with contrast and CSF findings are supportive, multiple sclerosis remains a clinical diagnosis.

4-8

Differential Diagnosis of IIH*

Highly Likely

Decreased Flow through Arachnoid Granulations

Scarring from previous inflammation (e.g., meningitis, sequel to subarachnoid hemorrhage)

Obstruction to Venous Drainage

Venous sinus thrombosis

Hypercoagulable states

Contiguous infection (e.g., middle ear or mastoid, otitic hydrocephalus)

Bilateral radical neck dissections

Superior vena cava syndrome

Increased right heart pressure

Endocrine Disorders

Addison's disease

Hypoparathyroidism

Obesity

Steroid withdrawal

Nutritional Disorders

Hypervitaminosis A (vitamin, liver, or isotretinoin intake)

Hyperalimentation in deprivation dwarfism

Arteriovenous Malformations

Probable Causes

Anabolic steroids (may cause venous sinus thrombosis)

Kepone (chlordecone)

Ketoprofen or indomethacin in Bartter's syndrome

Systemic lupus erythematosus

Thyroid replacement therapy in hypothyroid children

Uremia

Possible Causes

Amiodarone

Diphenylhydantoin

Iron-deficiency anemia

Lithium carbonate

Nalidixic acid

Sarcoidosis

Sulfa antibiotics

Causes Frequently Cited But Unproven

Corticosteroid intake

Hyperthyroidism

Hypovitaminosis A

Menarche

Menstrual irregularities

Multivitamin intake

Oral contraceptive use

Pregnancy

Tetracycline use

*Cases must meet the modified dandy criteria of IIH except that a cause is found.

From Wall M: Idiopathic intercranial hypertension. In Breen L, editor: Neurologic clinics 9(1):73-95, 1991.

4-9

Clinical Definition of IIH (Modified Dandy Criteria)

Signs and symptoms of increased intracranial pressure

No localizing neurologic findings (sixth cranial nerve palsies are allowed)

Normal neuroimaging (with the exception of an empty sella)

Opening pressure on lumbar puncture of greater

than 250 mm water, with normal CSF (protein may

be low)

No other cause of increased intracranial pressure present

4-10

Infiltrative Optic Neuropathies

Lymphoproliferative disorders

Leukemia

monocytic

acute myelocytic

acute lymphocytic

chronic lymphocytic

Lymphoma

Plasmacytoma

Multiple myeloma

Metastatic carcinoma (esp. breast and lung)

Carcinomatous meningitis (esp. breast and lung)

Inflammatory Disorders

Sarcoidosis

Systemic lupus erythematosus

Wegener's granulomatosis

Infectious

Tuberculosis

Cryptococcosis

Toxoplasmosis

Toxocariasis

Cytomegalovirus

Coccidiomycosis

Aspergillus

Lyme disease

4-11

Sarcoidosis

Sarcoidosis is a multisystem idiopathic granulomatous inflammatory disorder that frequently affects the eye, orbit, and intracranial visual system. The disease is commonly diagnosed in patients in their thirties and forties, but it can occur at any age. In the United States, sarcoidosis is at least ten times more prevalent in African-Americans than in Caucasians.

Pathologically, affected tissues are infiltrated with noncaseating granulomas. Although this disorder is clinically and pathologically similar to tuberculosis, no causative agent has been identified in sarcoidosis.

Although some patients with proven sarcoidosis are asymptomatic, others may exhibit severe systemic and neurologic consequences. Most patients present with constitutional symptoms: malaise, weakness, fever, weight loss, and diaphoresis. Pulmonary involvement is common, and is manifest as hilar and mediastinal adenopathy often evident with a routine chest radiograph. Lung parenchymal involvement can cause coughing, shortness of breath, and wheezing. Cutaneous manifestations include erythema nodosum, nodular granulomas, lupus pernio, and mucous membrane (including conjunctival) lesions.

Similar to hilar adenopathy, painless and symmetric pe-

ripheral lymphadenopathy is common. Other affected organs include the liver, spleen, parotid glands, muscles, heart, and central nervous system.

Potential ocular and orbital involvement includes granulomatous uveitis, as well as infiltration of the conjunctiva, extraocular muscles, lacrimal gland, and optic nerve.

Involvement of the central nervous system is designated asneurosarcoidosis and commonly affects the optic nerves, chiasm, and optic tracts. Other cranial neuropathies, especially facial nerve palsies, are also common. Meningeal or ventricular disease can cause elevated intracranial pressure and papilledema. Meningeal neurosarcoidosis can also have a mass effect with compression of adjacent structures; it may be difficult to distinguish from meningioma both clinically and neuroradiologically. Parenchymal disease can cause neuroendocrine disturbances (such as diabetes insipidus from hypothalamic involvement), encephalopathy, or white matter changes that mimic multiple sclerosis.

A diagnosis of sarcoidosis may be based on the physical examination, imaging studies (hilar adenopathy, brain MRI), or serologic tests (elevated ACE, hypercalcemia, hypergammaglobulinemia). In some cases, a lumbar puncture and CSF analysis may be needed to distinguish neurosarcoidosis from infectious and neoplastic processes. Pathologic diagnosis can be made by identifying affected tissues (examination, gallium scan, and other imaging) that may be biopsied (bronchoscopy, skin, lymph node, lacrimal gland, or conjunctival biopsy).

Sarcoidosis almost always responds promptly to treatment with intravenous or oral steroids; therefore, failure to respond to treatment should lead to questioning this diagnosis. Steroid sparing agents and surgical ther-

apy for the complications of sarcoidosis are occasionally required.

4-12

Common Toxic/Nutritional Optic Neuropathies

Drugs

Ethambutol

Rifampin

Isoniazid (INH)

Chloramphenicol

5-Flurouracil

Disulfiram

Toxins

Methanol

Ethylene glycol

Heavy metals

Tobacco and alcohol

Nutritional deficiencies

Thiamine (B_1)

Vitamin B_{12} (pernicious anemia)

Folate

MAJOR POINTS

Anterior ischemic optic neuropathy is a common cause of unilateral optic disc edema and sudden visual loss in patients more than 45 years old.

AION may be nonarteritic or secondary to giant cell

arteritis.

A prompt diagnosis and treatment of giant cell arteritis can prevent bilateral blindness.

When giant cell arteritis is suspected, an ESR should be performed and steroid therapy should be instituted immediately, with a temporal artery biopsy

arranged within a few days.

Optic neuritis is a cause of visual loss in young patients characterized by pain with eye movement and an optic disc that may be edematous or normal in appearance.

High-dose intravenous steroids should be considered when patients with optic neuritis have white matter changes visible on MRI.

Papilledema may be caused by intracranial tumors and ventricular obstruction, or it may be an idiopathic disorder in young obese females.

Papilledema should be initially investigated by a

blood pressure measurement, neuroimaging, and lumbar puncture (if imaging reveals no mass or

obstruction).

Chronic papilledema can cause profound visual field loss despite normal visual acuity; patients must be followed with serial perimetry.

A gradual, insidious decline in vision with optic nerve pallor suggest a compressive optic neuropathy such as a meningioma, orbital mass, or orbital Graves' disease.

Optic nerve gliomas in children are frequently associated with neurofibromatosis (type I) and commonly behave in a benign fashion.

Acute leukemic infiltrative optic neuropathy is an emergency; radiation therapy may be sight-saving.

The term neuroretinitis designates optic disc edema associated with macular edema (with edema residues that typically form a macular star), which is often the result of an infectious process.

Toxic and nutritional deficiencies cause progressive, bilateral, cecocentral scotomas.

Leber's hereditary optic neuropathy (LHON) is associated with specific point mutations in mitochondrial DNA and typically causes acute visual loss in one eye, followed within weeks by a similar event in

the other eye, usually of young males.

Trauma to the optic nerve can occur without fractures because the forces from blunt trauma to the brow or cheek are mechanically funneled to the orbital apex and optic canal.

Optic disc drusen can be associated with peripheral (not central) visual field defects.

4-19, cont'd

E, Four generations of this family are known or suspected to be affected by this autosomally dominant hereditary neuropathy (Kjer's). (1. the mother, 2. the daughter.);E>