NEUROLOGY BOARD REVIEW MANUAL

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Neuro-ophthalmology: Disorders of the Afferent Visual Pathway

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INTRODUCTION

The visual system is a fundamental nervous system component. Neuro-ophthalmologic problems present special challenges in regard to the physician’s knowledge of neuroanatomy and clinical examination skills. Viewing the fundus offers real-time inspection of the nervous system and its pathology. This view reveals a vast arrangement of neural structures dedicated to capturing, processing, and scrutinizing light. Given the evolutionary importance of vision, visual pathways occupy a great extent of the neurologic landscape. Thus, a keen understanding of vision is crucial for appreciating many, if not most, neurologic illnesses.

This manual, the first part of a 2-part review of neuro-ophthalmology, focuses on disorders of the afferent visual pathway and uses clinical cases to illustrate essential concepts guiding the physician to the location of pathology as well as the underlying process of disease. The afferent visual system includes the retina, optic nerve, optic tract, optic chiasm, and retrochiasmal pathways, including the optic radiations and the cortical/higher cognitive areas of visual representation. The efferent visual system, which will be the focus of the next manual, encompasses the pupil as well as the mechanism of ocular motility and cranial nerves involved in eyelid function.

DISEASE OF THE RETINA

CASE PRESENTATION

A 66-year-old woman with a history of hypertension and lower extremity deep vein thrombosis (DVT) presents to the emergency department (ED) after a 5-minute episode of vision loss in the right eye. The patient had been well until earlier that day, when she developed sudden-onset loss of vision from the right eye beginning in the upper visual field. She covered her right eye and observed that vision from her left eye was normal. The patient had no eye pain, change in cognition or language, weakness, or other difficulties. Spontaneous and rapid recovery of vision ensued, after which she noticed no visual or neurologic deficits.

- What is the most likely cause of this patient’s symptoms? What disorders are in the differential diagnosis?

DIFFERENTIAL DIAGNOSIS OF TRANSIENT MONOCULAR VISUAL LOSS

In order to establish diagnostic possibilities in this patient, the evaluation begins with localizing the site of pathology. The patient’s visual symptoms are consistent with transient monocular visual loss (TMVL), which may reflect pathology in various sites including the retina, optic nerve, and even the more posterior visual structures including the cortex. Given the brevity and acuity of her symptoms and the altitudinal pattern of visual loss, the most likely site of disease is the retinal arterial vessels. In this setting, the probable source of arterial disruption is atheroembolism from a stenotic ipsilateral internal carotid artery (ICA).

Vascular Causes

TMVL is most often considered a disease of the retina, and more specifically the retinal vasculature (eg, the ipsilateral ICA). A severe stenosis of the ipsilateral ICA is made more likely when the patient reports rapid onset of symptoms and TMVL lasting 1 to 10 minutes. Visual loss respecting either the horizontal or vertical meridian commonly occurs in this setting and also points to disease of the ipsilateral ICA, although alternative sources of embolization are possible. Patients may perceive a curtain being pulled over the eye. Despite a lack of persistent symptoms, retinal emboli may be seen on fundoscopic examination (Figure 1; see page 8).

Additional important causes of TMVL via arterial disease of the retina or optic nerve include giant cell arteritis (GCA), other ischemic optic neuropathies, retinal
vasospasm (which may be a migrainous phenomenon), and malignant hypertension. With these entities, adjunctive historical and examination findings must be sought. However, TMVL may be the only symptom, and characteristic findings to suggest a specific arterial disease may be absent. In the setting of GCA, a so-called 
arteritic ischemic optic neuropathy, patients may report transient visual disturbances induced by light or changes in position, since vessels may have fixed stenosis secondary to inflammation. Additional stigmata of GCA, such as headache, jaw claudication, fevers, sweats, and weight loss, may be present. In terms of nonarteritic ischemic optic neuropathies, disease of the posterior ciliary arterial vasculature (ie, anterior ischemic optic neuropathy [AION]) is the most likely culprit. In posterior ischemic optic neuropathy (PION), as well as some cases of AION, the fundoscopic examination may be normal. However, typical findings in AION include mild disc edema, disc pallor with splinter hemorrhages, and dilated capillaries (Figure 2; see page 8). Retinal migraine usually occurs in patients with a history of headache, but older patients may report pain-free episodes. Although “positive” symptoms may be present with migrainous events, they also may be seen in more ominous causes of TMVL. In migraine, the mechanism of TMVL is believed to be arterial vasospasm.

Venous disease of the retina, such as central retinal vein occlusion, also may rarely cause TMVL (Figure 3; see page 8). In the case patient, who has a history of DVT—as well as in any case of a young patient with vascular disease—a source of hypercoagulability should be sought.

Nonvascular Causes

Alternative causes of TMVL to be considered include a host of nonvascular ocular problems, such as glaucoma, uveitis, decreased tear film, and hyperglycemia. In these settings, visual complaints generally are vague, less sudden, or associated with alternative symptoms. For example, patients with dry eyes report improvement of visual disturbances with repeated blinking; those with rapid worsening of vision from glaucoma report eye pain and photophobia.

Other diagnostic considerations include nonischemic optic neuropathies (eg, optic neuritis) or a disruption of the posterior visual pathways. Regarding the latter entity, for example, patients often interpret a left homonymous visual disturbance as left eye visual loss. Further, portions of the primary visual cortex that represent monocular and not binocular vision exist. The anterior portion of the left striate cortex, for example, represents 30 degrees of central temporal vision in the right eye only. Optic nerve or nerve-head disease may be secondary to inflammation (optic neuritis) or raised intracranial pressure (ICP; papilledema). These nonvascular entities may present as transient visual loss, and although the history and examination may suggest a particular entity, differentiation from retinal vascular disease may be difficult.

Case 1 Continued

Examination in the ED reveals a well-appearing woman without skin lesions and with a normal cardiopulmonary examination, including normal blood pressure. Cognition, motor-sensory function, deep tendon reflexes (DTRs), and plantar responses are normal. Best-corrected visual acuity (BVA) shows 20/20 vision in both eyes and normal contrast sensitivity, color perception, confrontation visual fields, and Amsler grid test. Direct and consensual pupillary responses to light reveal equally round and reactive pupils, both constricting from 3 to 2 mm without afferent pupillary defects (APDs). The extraocular movements also are normal.

What additional tests might be helpful in narrowing the diagnostic possibilities?

EVALUATION

Dilated fundoscopy may reveal clues to various retinopathies or optic neuropathies, but a normal examination would not be unexpected in the setting of transient symptoms. Although a myriad of ocular conditions may present as transient visual disturbances, a crucial entity to consider and exclude is angle-closure glaucoma. Here, intraocular pressure may be normal in between episodes, and thus, a careful evaluation of the anterior chamber would be in order.

As the main diagnostic considerations include ischemic diseases of the retinal vasculature, a careful evaluation of the retinal and neck vessels is paramount as both visual loss and stroke risk are greatly increased in this setting. Fluorescein angiography may reveal problems with the retinal vessels not seen on fundoscopy, such as abnormal choroidal filling, delayed arterial filling, or occult arterial nonfilling. Computed tomography angiography (CTA), magnetic resonance angiography (MRA), and/or Doppler ultrasonography of the neck vessels are performed to specifically examine the ICA.

Next, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are checked to evaluate for GCA. As mentioned, in appropriate patients, a thorough evaluation for a hypercoagulable state may be necessary and includes a complete blood count (CBC); international normalized ratio; partial thromboplastin
time; factor V and prothrombin gene evaluation; lupus anticoagulant; anticardiolipin antibodies; and antithrombin III, protein C, and protein S activity. An investigation of traditional cerebrovascular/stroke risk factors includes an evaluation of lipids and fasting blood glucose. Assessment of homocysteine, lipoprotein(a), and cardiac biomarkers and electrocardiographic Holter monitoring also may be considered.

CASE 1 CONCLUSION

- If this patient had presented with central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO), how would the treatment have been different?

In the setting of CRAO or BRAO (Figure 4; see page 8), a standard of care does not yet exist for restoring vision. Previously described treatments include eyeball pressure or massage, anterior chamber paracentesis, topical β-blockers, hemodilution, aspirin, acetazolamide, pentoxifylline, systemic anticoagulation with heparin, intravenous fibrinolysis with thrombolytic agents, and laser thrombolysis. Most of these therapies have been reported with mixed results.

DISEASE OF THE OPTIC NERVE

CASE 2 PRESENTATION

A 49-year-old woman with a history of Crohn’s disease presents to the ED after 1 day of progressive visual loss in the left eye. The patient reports that she first noticed blurring of vision in the left eye; this was followed by severe and progressive visual loss over a period of 1 or 2 hours. Since then, her vision has worsened slightly. She can detect light and the shapes of large objects but cannot make out any details of the visual scene. Further, vertical and horizontal eye movements induce retro-orbital pain on the left. There is no apparent trauma or history of fevers, sweats, rashes, cough, dyspnea, language or cognitive trouble, weakness, new sensory changes, or gait disturbance. Past medical history is significant for an unexplained episode of left-sided body numbness 19 years ago, which lasted 4 days and for which she did not seek medical attention. Ten years ago, she underwent partial small bowel resection, which included a significant portion of the distal ileum.

Examination in the ED reveals a well-appearing but rather thin woman. The general examination is normal. Cognition and motor-sensory function are normal. DTRs are brisk throughout, slightly more so on the left side. The left toe is up-going. BVA is 20/20 in the right eye and 20/100 in the left eye. The red tip of the reflex hammer appears light pink through the left eye and deep red through the right eye. She cannot make out the lines on the Amsler grid test. Confrontational visual field testing reveals a large central scotoma in the left eye, which is later confirmed with computerized visual field testing. There is a left APD. The extraocular movements and fundoscopic examination are normal.

- What features of this patient’s clinical picture suggest an optic nerve problem?

CLINICAL CLUES TO OPTIC NEUROPATHY

Again, the evaluation begins with determining the site of pathology. Monocular visual loss in conjunction with painful eye movements suggests an abnormality of the optic nerve. The pattern of visual field defects often assists in further localizing the disease.

Optic neuropathies tend to present as generalized constriction, central defects (associated with disease of the central portion of the nerve), and/or defects following the nerve fiber bundles (arcuate, altitudinal, and nasal step defects). In the latter scenario, as the nerve bundles are essentially parallel with the horizontal raphe, nerve fiber bundle defects tend to respect the horizontal meridian. Disease of the optic nerves (when asymmetric) reliably will cause an APD, which is not typically seen in retinal disease unless the pathology is severe and diffuse. Metamorphopsia, as assessed by Amsler grid testing, would be atypical for an optic neuropathy and more typical of retinal disease. Additional clues to optic nerve pathology include dyschromatopsia (abnormal color vision) out of proportion to diminished visual acuity, both of which are commonly present.

Upon optic nerve head inspection, disc swelling with blurring of the disc margins, hyperemia (redness from capillary dilation), and disc pallor may be seen. Pallor (Figure 5; see page 8) denotes a chronic lesion (with axonal
loss), whereas disc swelling or elevation (from sluggish axoplasmic flow) and hyperemia indicate a more acute process. In many acute cases, however, the optic nerve examination may be unremarkable. A normal-appearing optic nerve head also may be seen when the pathology is confined to the posterior portion of the nerve. Localizing the precise site of optic nerve pathology, to the region of the cavernous sinus for example, is further considered when concomitant deficits are seen with eye movements or facial sensation (in the ophthalmic distribution of the trigeminal nerve). These additional abnormalities (not seen in the case patient) may be produced by either an expansive/infiltrative lesion of the optic nerve or an extrinsic/compressive lesion affecting both the optic nerve and the nearby structures.

• What is the differential diagnosis for this patient?

DIFFERENTIAL DIAGNOSIS OF OPTIC NEUROPATHY

In the setting of normal systemic blood pressure and intraocular pressures, both (angle-closure) glaucoma and malignant hypertension are essentially ruled out but are important entities to consider initially. Other important diagnostic considerations are as follows.

Inflammatory Causes

Given the high suspicion of optic nerve disease, the patient’s sex and age, her pain with eye movements, and the rapidity of onset imply active inflammation of the optic nerve (ie, optic neuritis). The most common cause of optic neuritis in this setting is via primary demyelination, which is often the first clinical event in patients with multiple sclerosis (MS).18,19

Other inflammatory optic neuropathies may occur in the setting of systemic lupus erythematosus (SLE)20–22 and sarcoidosis.23–24 Either condition may present in isolation or with typical features of the particular systemic disease, such as rash or arthritis in lupus and pulmonary symptoms in sarcoidosis. In sarcoid-associated optic neuropathy, there may be uveitis, visible granulomas of the optic nerve head, retinal vasculitis, or infiltrative-appearing lesions on magnetic resonance imaging (MRI). In lupus-associated optic neuropathy, concomitant transverse myelitis is not unexpected,21 while the optic nerve disease may be secondary to small-vessel disease (as in the case of antiphospholipid antibody syndrome)22 or primary demyelination.

In addition to autoimmune disorders, primary infectious disorders should be considered. These include systemic bacterial infections (Lyme disease [Borrelia species], syphilis [Treponema pallidum], cat scratch disease [Bartonella henselae], and tuberculosis [Mycobacterium tuberculosis]), spread of local infection via paranasal sinusitis, fungal or protozoal infections (cryptococcosis, aspergillosis, and toxoplasmosis), and various viral infections (HIV, cytomegalovirus, herpes simplex virus, and varicella-zoster virus). Many of the infectious optic neuropathies are accompanied by ancillary retinal or systemic findings. Immunosuppression is an important risk factor for some of these entities.

Ischemic Causes

As noted in the previous case, an ischemic optic neuropathy (eg, AION or PION) should be considered. Typically, patients with ischemic optic neuropathy are older than age 50 and have classic vascular risk factors. With AION, there is disc edema (and occasionally peri-papillary edema, hyperemia, and splinter hemorrhages), whereas fundoscopic findings are typically lacking in PION. Although GCA is a cause of PION, it must be considered in both AION and PION. In cases of suspected optic neuritis, AION is often a prime consideration due to the similarity of findings on history and physical examination. Features that are considered more common with AION than with optic neuritis include sudden painless visual loss, worst vision at onset, lack of progression, and fluctuation with position changes.

Other Causes

There are many other causes of optic neuropathy, including nutritional, congenital, and hereditary etiologies, but most of these are not likely in this patient given her acuity of symptoms. Although Crohn’s disease places her at particular risk for vitamin B12 deficiency, this entity typically presents as slowly progressive bilateral visual loss in addition to other signs commonly seen with optic nerve dysfunction (eg, dyschromatopsia, central field defects).25,26 In addition, a neoplastic process could cause optic neuropathy via compression (eg, meningioma, glioma, and metastases) or infiltration (eg, lymphoma, leukemia, and metastases) but would be considered less likely given the rapidity of this patient’s presentation. Finally, a host of toxins have a particular affinity for the white matter and often the optic nerve (eg, methanol); these should be considered with an appropriate exposure history.

• What additional tests should be considered?

EVALUATION

Gadolinium-enhanced MRI of the brain, with special attention to the optic nerves, helps to confirm a possible inflammatory lesion as well as evaluate for a possible infiltrative or compressive lesion of the optic nerve. It also
serves to evaluate the brain parenchyma in this particular setting. A similar rationale applies to obtaining spine MRI. In suspected cases of optic neuritis, multiple white matter lesions of the CNS (in locations characteristic of MS) may further support the diagnosis of a primary demyelinating disorder and may help predict the development of future demyelinating events.

Cerebrospinal fluid (CSF) evaluation is not always necessary when isolated optic neuritis is considered most likely, but it may be helpful in evaluating for other causes. In optic neuritis, the CSF may be normal or may show mild lymphocytic pleocytosis (usually < 10 cells/mm³), oligoclonal banding, and increased IgG synthesis.

In a patient with known autoimmunity, testing for an autoimmune cause of optic neuritis would be appropriate. In the case patient, this would mean an evaluation for SLE, which might include testing for ESR, CRP, antinuclear antibody, lupus anticoagulant, antiphospholipid antibody, and angiotensin-converting enzyme as well as a chest radiograph. A basic evaluation for a primary infectious etiology would include testing for syphilis (rapid plasma reagin), Lyme antibody, and perhaps HIV antibody; further evaluation (of the serum and/or CSF) for infectious causes should be guided by the history and examination. Although B₁₂ deficiency would not explain the case patient’s current syndrome, it could conceivably lower her threshold for visual symptoms and/or lessen her recovery. Thus, a serum B₁₂ level would be of use in this patient.

**CASE 2 CONCLUSION**

Gadolinium-enhanced MRI of the brain and spine shows hyperintensity (on short-tau inversion recovery [STIR] sequences) and enhancement with T2 signal changes of the left optic nerve (Figure 6; see page 8). Also, there are multiple T2-hyperintense lesions of the periventricular white matter, the middle cerebellar peduncle, and the cervical spinal cord (Figure 7; see page 9). Many of these lesions are T1-hypointense and do not enhance. A serum evaluation is unremarkable. A CSF evaluation is not performed.

- What is this patient’s prognosis for visual recovery, and is she at risk for further demyelinating events?
- How should this patient be treated?

The prognosis for visual recovery is good and not affected by current treatments. Most patients will report returning to baseline visual ability, but a small proportion will not have a full or good recovery. Patients of African origin and those with poor visual acuity on presentation may experience the worst prognosis. Visual improvement is expected to occur within 2 to 8 weeks and is hastened by intravenous steroids followed by oral steroids. Oral steroids alone seem to increase the recurrence rate of optic neuritis as compared with placebo.

In the setting of clinically isolated optic neuritis with a normal brain MRI, the risk for development of MS (at 5 or 10 years follow-up) has been shown to be up to 20%. Conversely, patients with optic neuritis who have multiple white matter lesions on MRI are at greater risk for progression to MS (up to 50%). Based on the case patient’s current optic neuritis, past history of hemisensory symptoms, and brain/spine MRI findings suggestive of MS, the diagnosis of MS is most likely. Thus, for the acute event and symptoms, a 3-day course of intravenous solumedrol followed by oral steroids may be given. Next, the patient can be started on interferon or glatiramer acetate therapy for prevention of future demyelinating events. In the setting of a normal MRI, disease-modifying therapy is usually held and the patient watched over time. In the future, if there is proof of dissemination of lesions (new demyelination attacks in a different region of the CNS), disease-modifying therapy is offered.

**DISEASE OF THE OPTIC CHIASM**

**CASE 3 PRESENTATION**

A 62-year-old man with a history of hypertension, coronary artery disease, and hypothyroidism presents to the neurology clinic with blurred vision and difficulty reading. His visual complaints began several months ago and were accompanied by constant, mild, and diffuse headaches. The patient says he has checked each eye separately and believes the visual disturbance exists in both eyes. At times, he has noticed possible double vision, but he is unsure of precipitating factors. The symptoms have been fairly constant (not paroxysmal or episodic) since their onset and have worsened somewhat.

Examination reveals a well-appearing and mildly obese man. The general examination is notable for a soft, left upper sternal border systolic ejection murmur and mild lower extremity edema. Cognition, motor-sensory function, DTRs, and plantar responses are normal. BVA is 20/40 in the right eye and 20/25 in the left eye. The patient misses 6 of 10 Ishihara color plates with the right eye and 3 of 10 with the left eye. The Amsler grid test is unremarkable. Confrontational visual field testing reveals a superior temporal quadrantanopia in the left eye. This finding is later confirmed with
computerized visual field testing, which also reveals a small central scotoma in the right eye. There is a right APD. The extraocular movements are normal. Fundoscopic examination (after pharmacologic dilation) reveals bilateral mild disc pallor.

• What features of this patient’s history and examination are useful clues to the specific location of pathology?

CLINICAL CLUES TO DISORDERS OF THE OPTIC CHIASM

Headache, blurry vision, and double vision raise concern about increased ICP, which may have many causes. Increased ICP is transmitted to and around the optic nerves, as the subarachnoid space surrounds the optic nerve for much of its course. Raised pressure prevents normal axoplasmic flow, with resultant stasis, papilledema, axonal loss, and visual degradation. In this setting, diplopia is often secondary to abducens nerve palsies (unilateral or bilateral). Here, diplopia worsens with far vision, which requires ocular abduction. However, this patient’s visual symptoms are consistent with pathologic processes at other sites as well, making them somewhat nonspecific. Cortical and/or vascular disturbances as seen in migraine, for example, may also manifest as such symptoms as headache, blurry vision, or diplopia. Further, patients with disturbances of the primary or visual association cortices may report vague symptomatology, making localization difficult.

In this case, the examination helps to shed light on the precise location of disease. First, defective color vision out of proportion to visual acuity deficits increases the likelihood of disease in the optic nerve or optic chiasm. Although primary retinal disease is possible, a normal Amsler grid test makes this less likely. The APD further supports the possibility of asymmetric disease of the optic nerve or optic chiasm. If the lesion were posterior to the optic chiasm and optic tract, the pupillary light reflex would be unaffected and there would be no APD. Because the pupillary light reflex involves afferent fibers from the retina to the optic chiasm and then the midbrain, lesions posterior to the optic tracts may produce marked visual disturbances, including blindness, but will not affect pupillary construction to light.

The abnormalities on visual field testing also suggest a lesion of the optic chiasm and/or the posterior portions of the optic nerve. Nerve fibers from the temporal retina (subserving the respective contralateral nasal visual field) travel in the lateral portions of the optic nerve and remain lateral as they enter the optic chiasm. Conversely, fibers from the nasal retina (corresponding to the contralateral temporal visual field) travel through the medial portions of the optic nerve and then cross near the midline to enter the contralateral portion of the optic chiasm. In both the nasal and temporal retinas, axons from the superior portion of the retina (representing the contralateral inferior visual field) remain superior, and the inferior fibers (representing the contralateral superior visual field) remain inferior. After the inferonasal retinal nerve fibers have crossed, they bend anteriorly into the posterior portion of the contralateral optic chiasm, forming Wilbrand’s knee. It should be noted that this classic description of Wilbrand’s knee has been challenged and attributed to artifactual changes. Since many lesions affecting the optic chiasm result from compression from below, the initial visual field defect is a bitemporal superior quadrantopia, because the crossing inferior nasal fibers are affected first. Lesion progression results in classic bitemporal hemianopia when the superior chiasmal fibers become involved. The pattern of visual field defects seen in the case patient suggests a lesion of the posterior right optic nerve and/or right anterior optic chiasm, with Wilbrand’s knee involvement. The resultant field defect is a junctional scotoma, which is an ipsilateral optic nerve–type defect and a contralateral superior temporal defect.

As noted, the patient also reports double vision, which is rare but well recognized with complete bitemporal defects. Here, there may be overlapping or misaligned nasal visual fields. Alternatively, patients with blurry or otherwise disturbed vision may interpret the visual defects as “double vision” despite lacking true diplopia. Although not seen in the case patient, various eye movement abnormalities may be seen with chiasmal disturbances, including see-saw nystagmus.

Finally, fundoscopic examination may be normal or abnormal depending on location, severity, and chronicity of the chiasmal lesion. Chronic compression of the chiasm with resultant bitemporal hemianopia may be accompanied by generalized atrophy or transverse band optic atrophy in both fundi. Band atrophy results from loss of axons (in the nasal macula and retina) subserving the temporal visual fields. The nasal macular fibers enter the temporal optic disc, and the nasal retinal fibers enter the nasal optic disc. Thus, transverse band atrophy results from degeneration of these 2 axonal sets.

• What is the differential diagnosis of a chiasmal lesion?

DIFFERENTIAL DIAGNOSIS

Chiasmal lesions may be subdivided into disorders of extrinsic chiasmal compression (Figure 8; see page 9)
Figure 1. Hollenhorst (cholesterol) plaque. Various types of embolic material may be seen on routine fundoscopic examination. Examples of various retinal emboli include cholesterol, fibrin, and platelets. The arrow points to a cholesterol embolus in the inferior retina of the case patient.

Figure 2. Anterior ischemic optic neuropathy. This fundus demonstrates disc edema with dilated capillaries and a splinter hemorrhage (arrow).

Figure 3. Central retinal vein occlusion. This fundus demonstrates disc edema and retinal and peripapillary hemorrhages, along with dilated and tortuous veins.

Figure 4. Branch retinal artery occlusion. This fundus demonstrates an occlusion of the superior retinal artery with accompanied ischemic superior retina. The arrows point at the demarcation between normal (darker) and ischemic (lighter) retinal tissue.

Figure 5. Previous optic neuritis with resultant optic pallor.

Figure 6. Optic neuritis. This coronal T2-weighted magnetic resonance imaging sequence shows an abnormal signal of the left optic nerve.
Figure 7. Multiple sclerosis (MS). (A, B) These T2-weighted axial magnetic resonance imaging (MRI) sequences of the brain show multiple white matter lesions (arrows) of typical location and quality for MS: (A) subcortical and periventricular white matter and (B) the middle cerebellar peduncle. (C) This T2-weighted sagittal MRI sequence of the cervical spine shows an additional white matter lesion at C3–C4.

Figure 8. Extrinsic compression of the optic chiasm. This coronal T1-weighted gadolinium-enhanced magnetic resonance imaging sequence demonstrates compression of the optic chiasm through upward compression of an enhancing sellar mass (arrow).

Figure 9. Sporadic Creutzfeldt-Jakob disease. This diffusion-weighted magnetic resonance imaging sequence shows classic brightening of the cortical ribbon (arrows).

Figure 10. Fundoscopic views of the optic nerves show (A) a normal optic disc and (B) papilledema. (C) This computed tomography scan shows right optic nerve head calcifications (arrow) as would be found with optic disc drusen. Fundoscopic views of the optic nerves show (D) a congenitally small and crowded optic disc and (E) a tilted optic disc.
and disorders intrinsic to the chiasm itself. Extrinsic compression is far more common and mainly stems from diseases of the sellar and suprasellar regions. Thus, detailed questioning related to the function of the pituitary-hypothalamic axis may uncover signs of deficiency or excess of growth hormone (GH), prolactin, oxytocin, gonadal hormones (follicle-stimulating hormone, luteinizing hormone), thyroid hormones, cortisol, and antidiuretic hormone.

It is also useful to group the possible diagnostic entities into diseases of the young or old. The pediatric and adolescent populations commonly suffer chiasmal-hypothalamic gliomas or craniopharyngiomas, whereas the common chiasmal disorders of adults are pituitary adenomas, meningiomas, craniopharyngiomas, and internal carotid aneurysms. Pituitary adenomas may be secretory or nonsecretory. Most are secretory and produce prolactin or GH. A host of chiasmal illnesses have no age predilection and include histiocytosis, sarcoidosis, and meningitis.

An additional consideration in the case patient with various vascular risk factors is chiasmal infarction. However, the progressive nature of the patient’s visual loss makes this less likely. Further, chiasmal infarction is generally uncommon owing to the rich blood supply from both the anterior and posterior circulations.

- **How should the diagnostic work-up ensue?**

Given the high probability of a chiasmal and sellar/suprasellar disturbance, gadolinium-enhanced MRI of the brain should be ordered, with special attention to the optic nerves, chiasm, and sellar/suprasellar areas. Since vascular malformation is a diagnostic possibility, MRA is also indicated. If imaging were to reveal a pituitary adenoma, for example, a comprehensive endocrinologic evaluation would be included, since treatment is dictated by tumor type.

**CASE 3 CONCLUSION**

On further questioning, the patient denies any gynecomastia, abnormal breast secretions, diminished libido, testicular atrophy, signs of hyper- or hypothyroidism, fatigue, light-headedness, skin darkening, polydipsia, or polyuria. Examination shows no signs of GH excess/acromegaly upon inspection of the hair, facial features, bony prominences, and skin. MRI of the optic nerves shows abnormal T2 signal without enhancement in the anterior portion of the optic chiasm. MRA shows a large (3 cm) right ICA-ophthalmic artery aneurysm. Neurosurgical consultation is obtained.

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**DISEASE OF THE RETROCHIASMAL/CORTICAL PATHWAYS**

**CASE 4 PRESENTATION**

A previously healthy 67-year-old man presents to the neurology clinic complaining of mild cognitive disturbances and difficulty with depth perception. The patient was well until 4 months prior, when he noticed that he could not “clear the cob webs (over his mind).” In the weeks since, he has experienced a slow progression of symptoms. He has great difficulty following written instructions in assembling a computer, a task that would normally not give him trouble. He says he also has difficulty judging the relative distance of objects, such as a nearby tree versus a far-off building. In addition, his family notes slowness of thought as well as new mild gait imbalance.

Examination reveals a well-appearing and athletic elderly man. The general examination is normal. The patient has difficulty with complex commands, and although he displays normally conversant language content, he has a delayed speech output. His attention, memory, calculation, praxis, and fund of knowledge are normal. He has difficulty recalling driving directions from his home to the local university where he has been employed as a professor for many years. When asked to describe an elephant’s appearance, he simply responds, “It is a large animal living in Africa.” When shown a complex visual scene, he accurately describes the individual objects presented but cannot report the overall theme.

Motor-sensory function and plantar responses are normal. There is right-sided upper and lower extremity dysmetria and hypoactive DTRs. The Romberg test is positive. The gait is wide-based, with moderate instability and stumbling to the right side. BVA is 20/20 in the right eye and 20/20 in the left eye. The patient misses 8 of 10 Ishihara color plates with the right eye and 9 of 10 with the left eye. Although he cannot identify the number on the color plate, he names the correct colors when asked to identify specific colored dots. The Amsler grid test is unremarkable. Confrontation visual field testing reveals full visual fields. Pupillary responses to light and extraocular movements are normal. Fundoscopic examination (after pharmacologic dilation) is unremarkable.

- **Where in the visual pathway may a disruption cause the visual and cognitive deficits noted in this patient?**
CLINICAL CLUES TO DISEASE OF THE VISUAL PRIMARY AND ASSOCIATION CORTEXES

Focusing on the visual symptoms alone, the problem likely lies within the visual cortices. Although visual loss is not unique to disease of the visual cortex, a host of visual difficulties are more specific to cortical disturbances. These include higher visual processes such as recognizing objects or faces, distinguishing colors, imagining a visual image, or mentally mapping out visual space. The deficits of the case patient all fall under this category. In this context, deficits may be subdivided into those belonging to the primary visual cortex along the banks of the calcarine fissure in the occipital lobes, or those of the association visual cortices, located in the occipitoparietal and occipitotemporal regions.

With disease of the primary visual cortex, the patient may have complete loss of vision in a quadrant or hemifield, depending upon the exact location of the lesion. Association visual cortical disease can broadly be separated into deficits in object or form analysis visual tasks (the “what” pathway of the occipitotemporal regions) and deficits in motion/spatial perception (the “where” pathway of the occipitoparietal regions). Because of overlapping geographic location and blood supplies, patients often have a combination of both primary visual and “higher” disturbances. Those with a right occipitotemporal disturbance, for example, may have a left superior quadrantopia in addition to object recognition difficulty when presented with an object to the “seeing” portion of the left hemifield.

The case patient reports difficulties in depth perception and in describing simple driving directions, despite preserved attention and memory. This implies disease of the “where” pathway. He also has difficulty imagining/a common animal and determining the overall theme of a visual scene (ie, simultagnosia). Although it is possible that the patient has a cortical disturbance of color vision, it is more likely that he misses the Ishihara color plates because of agnosia. In this setting, the patient focuses on the individual colored dots but cannot perceive the numerical digit formed by the dots’ arrangement. These problems entail disease of the “what” pathway. Since visual fields are intact, the primary visual cortex is undamaged. Thus, the patient probably has a diffuse pathogenic process affecting the visual association cortical areas of the temporal, parietal, and occipital lobes.

- What types of disorders affect visual association areas?

DIFFERENTIAL DIAGNOSIS OF VISUAL ASSOCIATION DEFICITS

The case patient’s history is ominous, with a progressive decline of cognitive abilities and visual perception with signs of cerebellar disease (or related/connected areas). Few disorders produce such a constellation of findings, and a prionopathy such as sporadic Creutzfeldt-Jakob disease (CJD) is most likely. Alternative considerations that may affect various cortical and motor/cerebellar areas include neurosyphilis, progressive multifocal leukoencephalopathy, Whipple’s disease, steroid-responsive encephalopathy (Hashimoto’s encephalitis), assorted cerebral vasculitides, posterior reversible encephalopathy syndrome (PRES), paraneoplastic encephalitis, bismuth intoxication, and various metabolic or toxic disturbances. Patients with acute deficits of higher visual function most commonly have suffered strokes. Although various posterior circulation strokes may produce such findings, this commonly occurs after acute systemic hypotension, which may induce watershed infarction of the bilateral occipitoparietal regions and may produce cortical blindness or Balint syndrome (simultagnosia, optic ataxia, and ocular apraxia). Finally, patients with numerous chronic degenerative disorders, such as Alzheimer’s disease or posterior cortical atrophy, also may present with or develop deficits of the visual association areas.

- How should the work-up proceed?

Given the possibility of PRES or a toxic-metabolic disturbance, the initial focus is on the blood pressure, possible offending medications, electrolytes, kidney function, and liver enzymes. Serum ESR, CRP, CBC, and a paraneoplastic encephalitis antibody panel should be considered. Next, a brain MRI with gadolinium and CSF analysis may reveal signs of inflammation or infection. The CSF can be sent for Venereal Disease Research Laboratory (VDRL) testing (to evaluate for neurosyphilis), 14-3-3 protein testing (an indicator of neuronal damage), and perhaps alternative infectious markers depending upon patient presentation.

CASE 4 CONCLUSION

The complete metabolic panel, CBC, and ESR/CRP are normal. On brain MRI, various regions of the cortical ribbon in the occipital, parietal, and temporal regions are bright on diffusion-weighted imaging (Figure 9, see page 9). There are no enhancing lesions. The CSF opening pressure, cell counts, glucose, and protein are normal. The VDRL test is negative. The
14-3-3 protein test is positive. Given the characteristic history, brain imaging, and unremarkable additional testing, the patient is believed to have sporadic CJD.

Over the next few months, the patient becomes progressively withdrawn and develops cortical blindness, despite an empiric trial of high-dose intravenous steroids. He dies 7 months after his first symptom. Necroscopy shows typical findings of sporadic CJD.

**Disease of Cerebrospinal Fluid Flow Dynamics**

**Case 5 Presentation**

A 25-year-old woman with a history of acne presents to the primary care clinic with headache and occasional episodes of flashing lights in the right or left eye. Medications include tetracycline for the acne.

As a child, the patient experienced a moderate to severe unilateral throbbing headache with nausea and vomiting every few months. In her late teenage years, these headaches abated. She was well until a few months prior to presentation, when she developed a mild, daily headache. The pain has been nonthrob- bing and diffuse but more focused behind the eyes. Although mild at first, the headaches have worsened and are now of moderate severity. Although she has periods of headache freedom, the pain persists for most of the day. The headache does not awaken her from sleep and is not altered in quality with changes in position or Valsalva maneuvers. She reports no nausea, vomiting, blurred vision, vertigo, weakness, or gait abnormalities. However, she has experienced occasional horizontal diplopia and episodes of flashing lights in both eyes. These episodes occur every couple days. She also reports an occasional “whooshing” sound in both ears.

Examination reveals a well-appearing and moderately obese woman. The general examination reveals mild acne on the face. Cognition, strength, sensation, coordination, DTRs, and gait are normal. Facial sensation, facial strength, hearing, voice quality, tongue movements, and sternocleidomastoid strength are also normal. BVA is 20/30 in the right eye and 20/25 in the left eye. Ishihara color plate, contrast sensitivity, Amsler grid test, and intraocular pressure evaluations are normal. Upon confrontation and formal visual field assessment, there is generalized constriction of the visual fields and enlarged blind spots in both eyes—this pattern is more severe in the right eye. Pupils are equally round and reactive to light without APD. Upon cover testing, there is a left esotropia, but ocular ductions are otherwise normal. Fundoscopic examination (after pharmacologic dilation) reveals bilateral optic nerve swelling. Disc margins are completely obscured in both eyes without disc hemorrhage or atrophy.

- What features of the history and examination are indicative of increased ICP?

**Clinical Clues to Elevated Intracranial Pressure**

As in case 3 (disease of the optic chiasm), the historical features in this case are nonspecific. The patient reports headache, flashing lights (photopsia), and a “whooshing” sound. At this point, prolonged and recurrent migraine headache would be considered in the differential diagnosis, as would an intracranial mass lesion or meningeal or optic nerve sheath irritation. In the latter scenario, an inflammatory optic neuropathy may explain the positive visual symptoms. Increased ICP is of concern, as it can be secondary to a host of intracranial processes including space-occupying lesions. In the case patient, new-onset and unremitting headache raises concern, as would additional features that might indicate raised ICP. These associated features may include worsening headache while lying flat with cough or Valsalva maneuvers or headache that awakens the patient from sleep.

As in many cases with nonspecific symptomatology, the examination serves to either focus the physician on a particular location of pathology or to reassure the physician and patient. In this case, 2 important findings indicate raised ICP: disc swelling and the abducens palsy. Generalized visual field constriction can occur with retinal disease, optic nerve pathology, or raised ICP. Given the additional signs of elevated ICP, generalized visual field constriction can be attributed to the ICP itself. Further, optic neuropathies often cause optic nerve–type central visual field defects, which would be uncommon with raised ICP alone. As noted previously, raised ICP alone can cause either bilateral or unilateral abducens palsies, the latter being a “false-localizing” sign. Although it remains possible, the patient’s raised ICP may be secondary to a mass lesion, for which there are no additional supportive examination findings, such as cortical, subcortical, or other brainstem signs.

- What are the causes of optic disc swelling?

An initial point of distinction is whether or not the optic disc swelling is the result of raised ICP. In this setting, the disc swelling is termed papilledema. In all other causes of disc swelling, the term papilledema is not used. Additional causes are outlined in case 2 and include vascular, inflammatory, infectious, neoplastic,
toxic, and metabolic optic neuropathies. Optic swelling may have an identical fundoscopic appearance whether from papilledema or via an optic neuropathy. In both cases, disrupted axoplasmic flow in the optic nerve ganglion axons is the cause of swelling at the optic disc. Because axoplasmic flow occurs at a very slow rate, swelling is not apparent in the acute phase of elevated ICP. Thus, it usually takes several days or weeks for papilledema to be evident, even in cases of acute, rapid, and large increases in ICP.52

Additional etiologies may also appear similar to papilledema and include a variety of congenital optic nerve abnormalities or variants. With these entities (eg, optic disc drusen, congenitally small and crowded optic disc, tilted optic disc), fundoscopic optic disc appearance is termed pseudopapilledema (Figure 10; see page 9).

**What is the most likely diagnosis in this patient?**

Although a symmetrical optic neuropathy (eg, bilateral optic neuritis) may be the culprit in this case, the history and examination support raised ICP (papilledema). Alternatively, obstructive (noncommunicating) hydrocephalus might exist in the case patient, but the possible causative mass lesion is not supported by the examination. The combination of young adult female, obesity, tetracycline, headache, and examination findings consistent with raised ICP point to idiopathic intracranial hypertension (pseudotumor cerebri).

**PSEUDOTUMOR CEREBRI**

In this disease, patients develop raised ICP and suffer headache and visual loss in the absence of a space-occupying mass lesion.53–57 In some, the disease course is self-limiting and remits in a matter of months. In others, the headache is chronic and debilitating, while the visual loss is insidiously progressive. As in the case patient, photopsia and tinnitus can be seen. Additional symptoms may include chronic or transient blurred vision, neck stiffness, pain with eye movements, diplopia, nausea, and vomiting.58 Lower motor neuron facial palsies also have been reported,59 as have eighth nerve palsies, but these are uncommon. Like abducens palsies, these too are presumably from nerve stretching in the setting of raised ICP, although other mechanisms have been proposed. Apart from the abducens (and perhaps facial or eighth nerve palsies), additional neurologic deficits are absent.

When sixth, seventh, or eighth nerve palsies are present, especially in the setting of additional signs of raised ICP, the examiner focuses attention on the pons and fourth ventricle. The case patient has generalized visual field constriction and enlarged blind spots, both of which are common in this entity, as are nasal defects.50 Early on, visual acuity is often preserved, while papilledema is nearly universal.58 As the disease progresses, acuity worsens and optic disc atrophy may develop.

Although the cause is unknown, arachnoid villi dysfunction and resultant decreased CSF absorption may be the offender. However, the cause is essentially undetermined and could be multifactorial. A host of pathogenic mechanisms have been studied and include parenchymal edema, increased cerebral blood volume, excessive CSF production, and venous outflow obstruction59 as well as a local optic nerve compartment syndrome.50,60 Further, in order to be termed “idiopathic,” alternate causes of raised ICP and dysfunctional CSF absorption (eg, cerebral venous sinus thrombosis, arachnoid granulation disease via remote meningitis, vitamin A intoxication, and CSF hyperviscosity) must be ruled out. Various endogenous and exogenous factors have been proposed to play a role in the development of raised ICP and the pseudotumor cerebri syndrome. These include corticosteroids, corticosteroid withdrawal, various antibiotics (eg, tetracycline), lithium, cyclosporine, exogenous GH, pregnancy, thyroid disease, anemia, respiratory diseases, and various autoimmune illnesses.58 The precise relationship between the proposed causative mechanism and ICP is not clear and may be coincidental in many cases.

To further elucidate the diagnosis, neuroimaging and CSF analysis and pressure are indicated. CSF pressures greater than 25 cm of H₂O are expected. A variety of neuroimaging findings have been described in idiopathic intracranial hypertension, including an empty sella, optic nerve sheath dilation, and optic disc elevation (Figure 11).15

**CASE 5 CONCLUSION**

The patient undergoes gadolinium-enhanced brain MRI, which is normal. Lumbar puncture
reveals an opening CSF pressure of 50 cm of H₂O. Routine CSF analysis of cell count, total protein, and glucose are normal. The patient is started on acetazolamide, an agent to decrease CSF production. She is followed closely over the next year. Her visual signs and symptoms and headache resolve within 6 months.

**SUMMARY**

As illustrated by the cases presented, in order to assess the most anterior portions of the afferent visual pathway, precise knowledge of the posterior afferent pathway is required. Similarly, an appreciation for any one particular portion of the afferent visual pathway is needed to accurately assess any other component of the pathway. As will be discussed in the next manual in this series, the same concept holds true for the efferent visual system. These demands placed on the examiner present a challenge to diagnosis and treatment, requiring not only detailed knowledge of the visual pathways but also the adjacent neighboring structures. Since the visual pathways are so widely represented in the CNS, these structures essentially include the entirety of the brain. Thus, neuro-ophthalmologic cases are integral to the clinical practice of neurology and are rewarding to the physician who is able to solve the puzzle and initiate treatment that may lead the way to recovery.

**REFERENCES**


pseudotumor cerebri. Follow-up of 57 patients from five to 41 years and a profile of 14 patients with permanent severe visual loss. Arch Neurol 1982;39:461–74.
