



4 Neuro Conditions NOT TO BE MISSED

What do a drooping eyelid, a dilated pupil, an in-turned eye, a sore scalp, jaw pain, and growing feet have in common? They are among the possible symptoms or signs of neuro-ophthalmic conditions that can, at worst, threaten sight or life—and the ophthalmologist may be on the front line as the first physician to see the patient. Would you remember what to look for?

Four neuro-ophthalmologists provide expert advice on “don’t miss” conditions that every clinician should know about. Learn from their key points on examination, testing, and imaging for timely diagnosis or referral.

Pupil-Involving Third Cranial Nerve Palsy: Think the Worst First

By Annie Stuart, Contributing Writer

“A pupil-involving third cranial nerve palsy is one of the true emergencies in neuro-ophthalmology,” said Michael S. Vaphiades, DO, professor and chief of neuro-ophthalmology and electrophysiology services at Callahan Eye Foundation Hospital at the University of Alabama in Birmingham. That’s because it may signal an aneurysm, which could rupture and lead to a subarachnoid hemorrhage—a potentially fatal event.

The third cranial nerve, also known as the oculomotor nerve, supplies several of the extraocular muscles and the levator muscle as well as the ciliary muscle and iris sphincter. Thus, disorders of this nerve may have varied presentations, including ptosis, diplopia, ocular movement disturbances, and pupillary abnormalities. The ophthalmologist’s time-critical task is differentiating between compressive—possibly indicating an aneurysm—and noncompressive etiologies for third cranial nerve palsy.

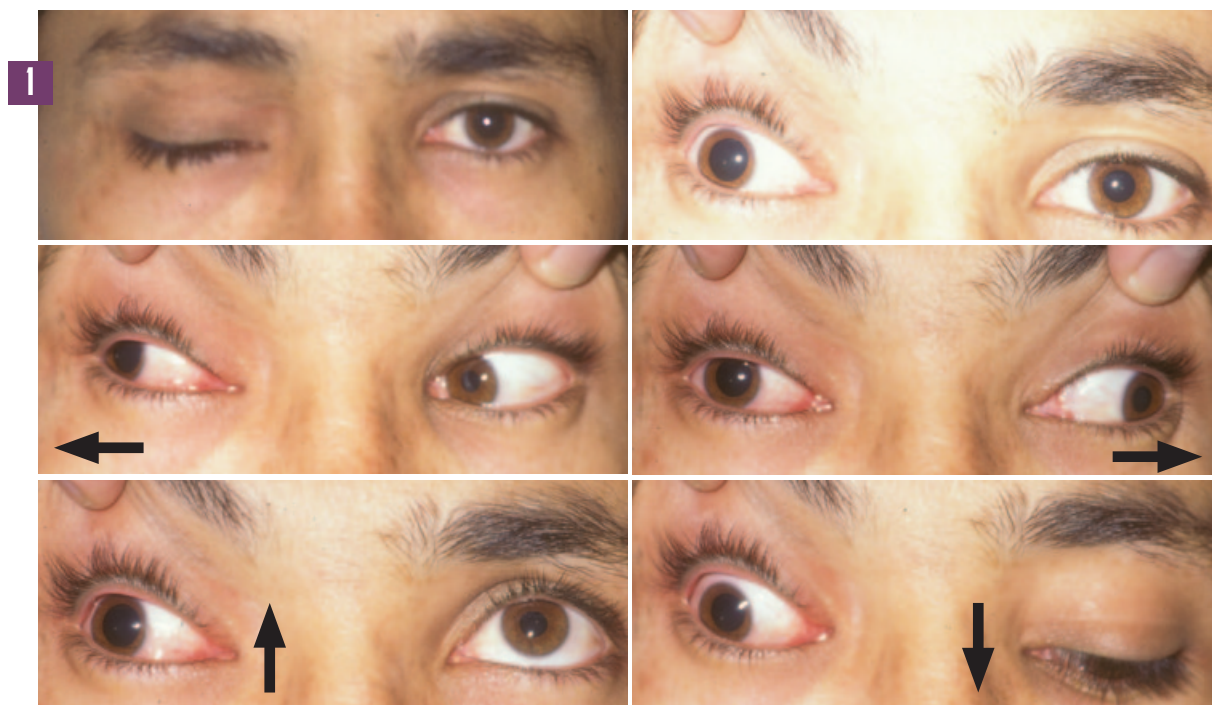
The pupil’s lessons. The classic “rule of the pupil” states that when aneurysms compress the oculomotor nerve, the iris sphincter will be impaired, leading to a sluggishly reactive or dilated pupil, said

Dr. Vaphiades. If the pupil is entirely spared in the setting of a complete ophthalmoplegia and ptosis, the oculomotor nerve palsy is usually due to a local infarction.

But the rule does not apply if the extraocular motor palsy is incomplete; it must be applied with caution to patients who are less likely to have vasculopathic risk factors or in whom an inflammatory or neoplastic cause is likely, he added.

To further confound the rule, posterior communicating artery (PCOM) aneurysms may present initially with normal pupils. Conversely, pupillary involvement can occur with vasculopathic oculomotor palsies, demonstrating anisocoria usually 1 mm or less but sometimes as great as 2.5 mm, said Dr. Vaphiades. “In addition, both intracranial aneurysms and vasculopathic oculomotor palsies may cause severe headache, further confusing these two entities,” he said. “So I always think of the worst first when it comes to third cranial nerve palsies, whether the pupil is involved or not.”

Other conditions to consider. Besides an aneurysm and vasculopathic etiology, other possible



COMPLETE THIRD-NERVE PALSY. (1) A 20-year-old man with a compressive right pupil-involving third cranial nerve palsy from a right PCOM aneurysm. The right eye is “down and out” with complete ptosis and a fixed, dilated pupil. (Arrows indicate direction of gaze.)

causes of third nerve palsy with pupil involvement include:

- Giant cell arteritis (GCA)
- Pituitary apoplexy
- Demyelinating disease (e.g., multiple sclerosis)
- Midbrain infarction
- Oculomotor nerve schwannoma/meningioma
- Brain metastasis
- Trauma
- Ophthalmoplegic migraine

Myasthenia gravis may also mimic a third cranial nerve palsy, but the pupil will never be involved, added Dr. Vaphiades.

DIAGNOSING THIRD CRANIAL NERVE PALS

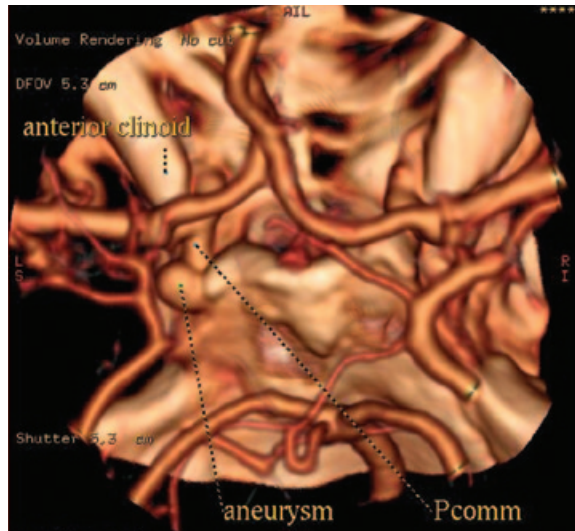
Whether you assess the patient yourself or refer to a neuro-ophthalmologist, documentation of an acute or progressive process is critical, said Dr. Vaphiades. An acute headache ratchets up the risk even more, pointing to a possible aneurysmal leak or rupture. This, along with stiff neck, nausea, and loss of consciousness, is a typical finding for a subarachnoid hemorrhage.¹

Ocular examination. With all new patients, Dr. Vaphiades conducts a standard history and exam, including checking eyelid position and evaluating the pupils—for symmetry, size, reactivity, and presence of a relative afferent pupillary defect—before administering dilating drops.

“The ophthalmic exam must also include investigating the ‘real estate’ in and around the third nerve,” said Dr. Vaphiades. This includes checking ocular motility to evaluate the fourth and sixth cranial nerves, as well as assessing corneal sensitivity and facial sensation innervated by the fifth nerve. “With complete third cranial nerve palsy, the eye has complete ptosis and is ‘down and out,’ moving only in the direction of the spared oculomotor nerves,” he said (Fig. 1).

Blood tests. Dr. Vaphiades recommends tailoring blood tests to the clinical situation. For example, you may need stat creatinine (to rule out impaired renal function before ordering a computed tomographic angiogram [CTA]); stat sedimentation rate, complete blood count, metabolic panel including glucose, and C-reactive protein (for suspected GCA); or cholesterol/triglycerides (for suspected vasculopathic cause).

Imaging. “If I suspect an aneurysm, I order an emergent CTA,” said Dr. Vaphiades, adding that he usually schedules same-day neuroimaging even for vasculopathic suspects. Concern has been raised about the cost-effectiveness of imaging all such patients. He said that if third nerve palsy is partial in



ANEURYSM UNMASKED. (2) CTA reveals a 7-mm aneurysm of the left posterior communicating artery.

any way, he strongly recommends neuroimaging, including brain magnetic resonance angiography (MRA) or CTA. For patients with a complete motor third nerve palsy, including complete ptosis and normal pupil, imaging remains controversial.

His preferred imaging modality is CTA; in particular, its maximum intensity projection (MIP) images not only show the vascular supply, he said, but also reveal the brain better than a conventional CT scan because of its thin slices and excellent resolution. With this technology, “It’s almost like you’re getting two studies in one.”

Dr. Vaphiades reserves noncontrast MRA for patients who are pregnant, have impaired renal function, or can’t tolerate the contrast dye used for CTA.

Further testing as needed. “CTA should detect aneurysms as small as 3 mm in size,” said Dr. Vaphiades. If CTA results are equivocal, the next step is a lumbar puncture to check for blood in the cerebrospinal fluid and conventional digital subtraction angiography—the gold standard for confirming the presence of an aneurysm.

MANAGING THIRD CRANIAL NERVE PALS

If the diagnosis is an aneurysm, the patient is immediately admitted for neurosurgical clipping. After the surgery, both neuro-ophthalmology and neurosurgery may follow the individual on an outpatient basis, said Dr. Vaphiades.

¹ Vaphiades MS, Horton JA. *Surv Ophthalmol.* 2005;50(4):406-410.

Anterior Ischemic Optic Neuropathy: High Stakes and Quick Decisions

By Marianne Doran, Contributing Writer

Encountering a patient with signs of anterior ischemic optic neuropathy tests the mettle of any ophthalmologist. The clinician must be able to quickly determine whether the patient has arteritic anterior ischemic optic neuropathy (AAION) or nonarteritic anterior ischemic optic neuropathy (NAION). NAION does not require immediate treatment or a specific intervention. AAION, however, is associated with giant cell arteritis—an ophthalmic emergency in which a missed diagnosis can be devastating.

“The single most important task in evaluating a new case of anterior ischemic optic neuropathy is to recognize the 10 percent or so of patients who have an arteritic condition,” said Nicholas J. Volpe, MD, professor and chairman of ophthalmology at Northwestern University in Chicago. “These patients have about a 75 percent risk of going blind in the other eye within days if it is not recognized and treated. To avoid that worst-case scenario, if you have a high suspicion of giant cell arteritis, you should send the patient to the emergency room for the lab workup and, potentially, immediate parenteral steroid treatment.”

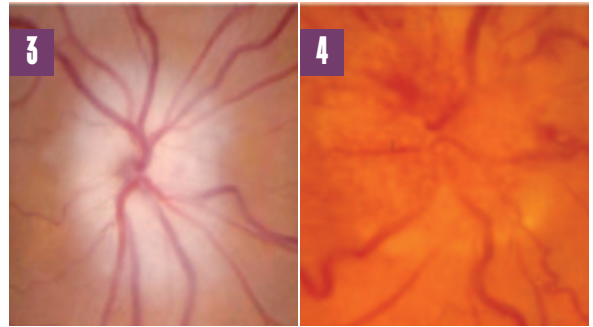
DISTINGUISHING AAION FROM NAION

The ophthalmologist must go through a series of steps to rule out AAION. Dr. Volpe noted that the arteritic form is more common among lightly pigmented individuals and rarely occurs in people younger than age 50 or 55 (the mean age is 70). He added that the patient may present with generalized malaise or muscle pain, but the most important additional signs are jaw claudication, headaches, and scalp tenderness. “If these are present in any form in the patient’s history, they raise the stakes much higher for arteritic ischemic optic neuropathy,” Dr. Volpe added, however, that about 25 percent of AAION patients have no prodromal symptoms.

In contrast, the mean age for NAION is 60. NAION arises with no warning and no prodrome, either systemic or ocular. “With these patients, one moment they are fine, but the next moment they have a problem,” Dr. Volpe noted. “They often have some risk factors, including diabetes and possibly elevated lipids and hypertension—but diabetes is the only generally accepted risk factor.”

Top five AAION findings. Dr. Volpe listed the key findings that point to a diagnosis of AAION:

- Severe vision loss to counting fingers or worse
- Chalky white swelling of the optic nerve (Fig. 3; compare with hyperemic swelling in NAION, Fig. 4)



OPTIC NERVE DIFFERENCES. (3) AAION. The optic nerve swelling is characteristically chalky white. (4) NAION. The optic nerve swelling is hyperemic.

- Evidence of retinal ischemia (i.e., cotton-wool spots or retinal artery occlusion)
- Abnormalities in perfusion of the choroid on fluorescein angiogram
- Abnormal exam of the temporal artery under the skin of the scalp

“These are the five things we think about when we look at these patients.”

Three tests for patients over 50. According to Dr. Volpe, every patient with anterior ischemic optic neuropathy who is over age 50 should have three stat laboratory tests: sedimentation rate, C-reactive protein, and platelet count. “Generally, elevation of any two of these increases the likelihood of arteritic ischemic optic neuropathy a great deal,” he added. “When in doubt, the ophthalmologist should not hesitate to treat the patient with steroids while he or she is trying to figure this out. If the suspicion is high, I would prefer that the patient be on steroids, even if unnecessarily, for up to four days while waiting for the test results.”

Biopsy if indicated. The history, exam, and laboratory findings determine whether the patient should have a biopsy of the temporal artery. Dr. Volpe emphasized that steroid treatment should not be delayed while waiting for a biopsy because treating the patient for several days will not affect the biopsy’s accuracy.

MANAGING AAION

Dr. Volpe said that general ophthalmologists can certainly diagnose AAION and initiate treatment, but they may want to involve a neuro-ophthalmologist in decision making about biopsy and chronic steroid

use. Once the diagnosis is established, he said, it is not unreasonable for an ophthalmologist to work in conjunction with an internist or a rheumatologist to manage a patient with giant cell arteritis.

WHAT ABOUT PATIENTS WITH NAION?

The nonarteritic form currently has no specific treatment, although some experts will put patients on systemic steroids, particularly if the condition is progressive. Identification of risk factors is important. “Ophthalmologists have tried to elicit a few historical points in these patients,” Dr. Volpe noted, “including risk factors such as diabetes, hyperlipidemia, and hypertension, as well as a history of sleep apnea.” The ophthalmologist might want to recommend that the patient strive for better management of these conditions.

A controversial issue is whether the use of phosphodiesterase type 5 (PDE5) inhibitors, including

sildenafil, tadalafil, and vardenafil, increases the risk of NAION. “We are now obligated to ask patients whether they had used erectile dysfunction drugs around the time of their event,” Dr. Volpe said. “Although the association is unproven, if they did use ED drugs, most of us will tell them not to use them in the future.”

MIMICKING CONDITIONS

Certain conditions can mimic anterior ischemic optic neuropathy. In a younger patient, for example, the profile for ischemic optic neuropathy overlaps that of optic neuritis. The same is true for neuroretinitis and other inflammatory or infiltrative conditions.

Dr. Volpe warned that as soon as the case seems to be progressing, involves pain, or is associated with atypical disc findings, a more detailed workup is indicated, including an MRI scan and blood workup for systemic inflammation and multiple sclerosis.

Horner Syndrome: Red Flags for Systemic Disorders

By Miriam Karmel, Contributing Writer

The patient who presents with a droopy eyelid, miosis, and anhidrosis on one side is probably not in danger of losing vision. But those telltale signs of Horner syndrome are red flags for possible underlying malignancy, stroke, or aneurysm.

More commonly, though, the underlying cause is benign, said Randy Kardon, MD, PhD, professor of ophthalmology and director of neuro-ophthalmology at the University of Iowa and director of the Iowa City VA Center for Prevention and Treatment

of Visual Loss. Previous neck or open heart surgery or cluster headaches, for example, might have caused damage along the sympathetic nerve pathway and triggered Horner syndrome.

But with Horner, the physician must always suspect the worst.

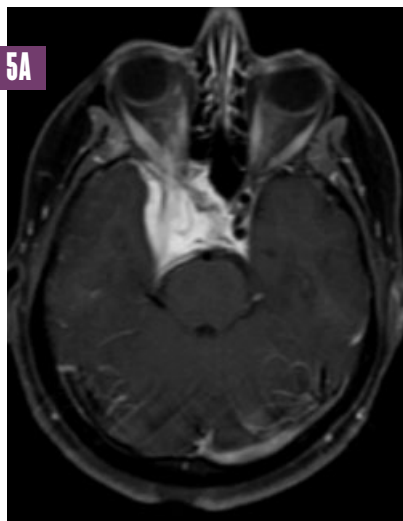
DIAGNOSING HORNER SYNDROME

Horner syndrome results from a lesion somewhere along the pathway of a paired three-chain nerve in

the sympathetic nervous system. The physician’s job is to find that lesion.

The first step is to recognize the syndrome. The classic presentation includes ptosis of the upper and lower eyelid, anhidrosis on the affected side, and pupil dilation lag after abrupt reduction in illumination (the affected pupil is much slower to dilate).

But it’s possible to misdiagnose Horner syndrome as Adie’s tonic pupil, physiologic



LOCALIZING THE LESION. (5A) A 52-year-old woman with a known cavernous sinus meningioma developed new Horner syndrome. (5B) Pupils at baseline. (5C) Dilation of right pupil after hydroxyamphetamine identifies the lesion as pre-ganglionic and, thus, unrelated to the meningioma.

anisocoria, a reaction to topical brimonidine, or pseudoexfoliation syndrome. Testing with 0.5 percent apraclonidine in both eyes will help confirm the diagnosis: In Horner syndrome, the affected pupil will dilate and the eyelid will sometimes elevate in response to apraclonidine, while the unaffected eye will change minimally, if at all. In infants six months of age or younger, cocaine testing should be used instead because apraclonidine can penetrate the blood-brain barrier and cause respiratory depression.

IDENTIFYING THE UNDERLYING CAUSE

History. Once Horner syndrome is confirmed, Dr. Kardon tries to establish the date of onset, sometimes resorting to family pictures. “Is it new or has it been there for years? The new ones are more worrisome,” he said. A history also includes questions about head or neck trauma, such as accidents or surgery that might have damaged the sympathetic nerve.

Localizing the lesion. Most patients with Horner syndrome get an MRI. But unless it’s an emergency, Dr. Kardon prefers to wait until he has run a second pupil test, this time with topical hydroxyamphetamine. (If cocaine was used to diagnose Horner, three days should elapse before the hydroxyamphetamine test. With apraclonidine, testing can be done the next day.) The hydroxyamphetamine test differentiates between Horner caused by damage along the first or second nerves in the chain (preganglionic Horner) and that caused by a lesion in the last nerve in the chain (postganglionic Horner). If the location is preganglionic, the affected pupil will dilate, but if postganglionic, the pupil will not change.

This distinction makes it easier to pinpoint where to direct the imaging. Some doctors order an MRI covering the entire sympathetic pathway, Dr. Kardon said. “The problem with that is it costs more, because you’re imaging a larger area of real estate. It also makes it uncertain where to look on an MRI. If the lesion is small and you’re not sure where along the chain to focus, it can be missed during reading of the scan. That’s why I use the hydroxyamphetamine test.”

A case in point. The case of a 52-year-old woman who came to Dr. Kardon after developing Horner syndrome highlights the importance of the hydroxyamphetamine test (Fig. 5). She had previously been diagnosed with a benign cavernous sinus meningioma that caused a sixth nerve palsy with double vision. This history suggested that the new Horner syndrome was caused by a lesion along the postganglionic sympathetic nerve at the site of the meningioma, Dr. Kardon said. But it wasn’t. “The hydroxyamphetamine test showed it was in a preganglionic

location. So we imaged her. Our image showed that she had a metastatic breast cancer, which had not yet been diagnosed.”

WHAT’S THE WORST IT CAN BE?

Malignancy. “Everyone’s concerned about neuroblastoma when they see a child with this syndrome,” Dr. Kardon said. Although it’s treatable, it can be deadly if not diagnosed early.

In adults, Horner may be caused by tumors occurring along the sympathetic chain, including lung tumors, thyroid cancers, and metastatic tumors.

Stroke. The first nerve of the three-nerve chain travels along the brain stem, the lower part of which is the medulla. Horner syndrome may signify a stroke in the lateral part of the medulla. “These patients can be walking and talking, and it’s not always obvious that they have a stroke,” Dr. Kardon said.

Vascular dissection. A patient may present with pain on the side of the face that can go into the ear or jaw and is sometimes mistaken for a toothache. But there could be a carotid dissection—a tear in the artery causing bleeding that compresses the postganglionic sympathetic fibers. A carotid dissection may cause a small clot to form, which can break off and lodge in the brain. Patients should be carefully monitored for signs of stroke.

Aneurysm. This potentially lethal vascular problem may occur in the carotid artery farther up in the brain. As the aneurysm expands, it may compress the nerves and cause a sixth nerve palsy and Horner syndrome. Patients may present with double vision and Horner.

WHEN NOT TO WORRY (TOO MUCH)

Cause unknown. Sometimes you don’t discover the underlying cause, Dr. Kardon said. For example, a problem may be localized to the preganglionic nerves, but the imaging is negative. In such cases, Dr. Kardon reassures the patient that he’s not seeing the cause. “But we don’t say, ‘Goodbye, have a good life.’ If the level of uncertainty is significant, then the patient is followed for at least another year to make sure nothing else crops up to make us want to reimagine the patient.”

As for the ophthalmologist, Dr. Kardon advises: When in doubt, make a referral to a neuro-ophthalmologist.

A happy ending. Some cases are crystal clear. A 50-year-old man was on his honeymoon in Holland when he slipped and fell on a dock. Prior to the trip he had a checkup and was declared fit. But the morning after the fall, he noticed that his right eyelid was drooping. He also experienced pain on the right side

of his face that was so severe he cut the honeymoon short. Back home he went to his dentist, who extracted a tooth. But the pain persisted, as did the droopy lid. After noticing a change in his pupil, he saw Dr. Kardon. An MRI revealed a right carotid dissection, probably related to his fall. Dr. Kardon put the patient on antiplatelet medication to reduce the chance of clot formation. The man weathered the episode

without a stroke, and the pain eventually resolved.

Bottom line. Be vigilant in making the diagnosis and looking for the underlying cause, Dr. Kardon said. “Even if the actual syndrome doesn’t cause much dysfunction, it’s a red flag that something serious may be going on. The ophthalmologist may be the first one to bring it the attention of other specialists.”

Pituitary Adenoma: Recognize the Visual Field Patterns

By Miriam Karmel, Contributing Writer

Before the advent of MRI and sophisticated hormonal blood tests, pituitary adenomas were often diagnosed by the ophthalmologist. “Nowadays, far fewer are discovered by the ophthalmologist because we have other tests that will find them,” said Karl C. Golnik, MD, professor of ophthalmology, neurology, and neurosurgery, Cincinnati Eye Institute, University of Cincinnati.

DIAGNOSING PITUITARY ADENOMA

Depending on the patient’s complaint—headache, hormonal changes, or visual disturbance—the initial diagnosis may be made by a neurosurgeon, an endocrinologist, or an ophthalmologist. Ultimately, however, the three specialties work together to treat the patient.

Often the finding is incidental, as, for example, when an MRI is ordered for a headache or injury. Or the patient may present with a hormonal problem. Then the ophthalmologist gets involved to determine if vision is affected.

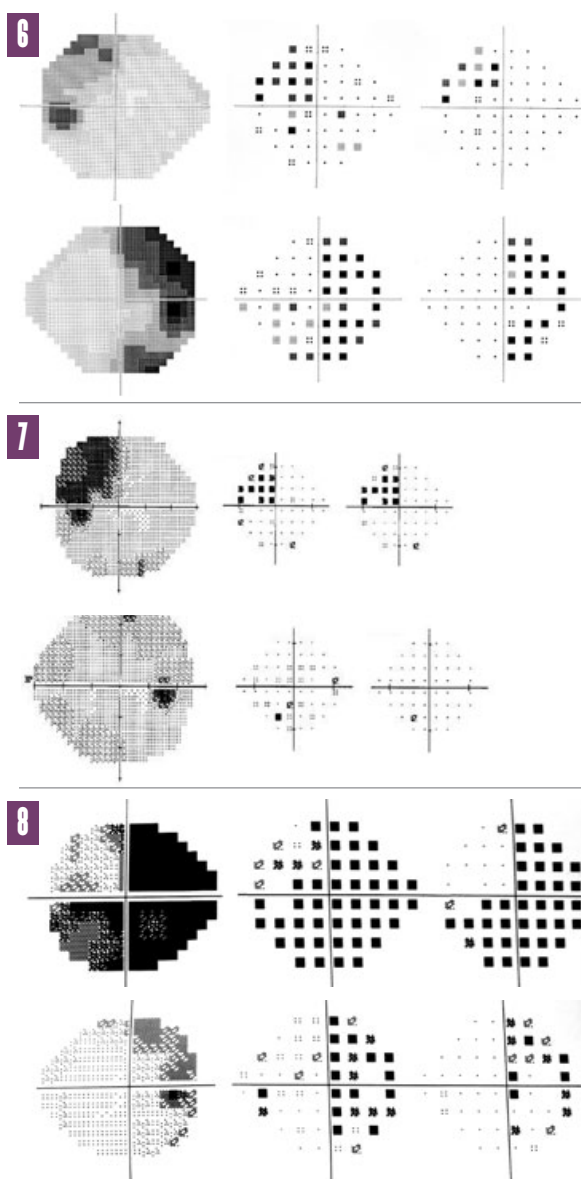
The good news is that pituitary adenomas do not grow quickly, and they’re usually benign, said Dr. Golnik. “They don’t spread. They don’t kill you.”

But they can disturb vision and even lead to blindness by putting pressure on the chiasm or other parts of the visual system in that area, such as the optic nerve and optic tracts.

Visual field testing is essential. “Automated perimetry is a must,” Dr. Golnik said. It is also important to assess visual acuity, pupils, and optic disc appearance.

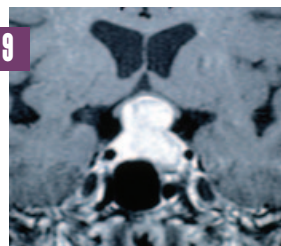
Bitemporal defect is a classic finding. The classic visual field presentation is “a slam dunk,” he said. “It’s not going to create any confusion.” The gray scale in the printout is shaded black right down the middle: In the right eye, the shading is to the right; in the left eye, shading is to the left.

Don’t overlook uncharacteristic visual fields. “But remember that pituitary tumors can present



SUSPICIOUS FIELDS. (6) Asymmetric bitemporal defects. (7) Unilateral defect caused by compression anterior to the chiasm. (8) Junctional scotoma.

in more ways than just the classic bitemporal visual field defect,” he said. For example, in a nonclassic visual field, one side may look bad, while the other side shows only a mild defect (Fig. 6). “It’s still a bitemporal field defect, but not complete. The asymmetry can throw people off. In some cases, one might even



SUSPICION CONFIRMED.
(9) MRI reveals a pituitary adenoma.

see a unilateral temporal defect if the compression is occurring at the distal optic nerve just before the chiasm [Fig. 7].”

Another variation of visual field sometimes seen in pituitary adenoma is the so-called “junctional scotoma,” or anterior chiasmal syndrome (Fig. 8). In this situation, there is central loss of vision due to op-

tic nerve compression in one eye and temporal loss in the other eye due to chiasmal compression.

Dr. Golnik’s concern is that an ophthalmologist could miss the diagnosis by not recognizing that these unusual visual field presentations may be related to pituitary tumor. In such cases, especially if the eye looks healthy, it’s tempting to do nothing and tell the patient to return in six months. But he warned that a delayed diagnosis may lead to serious vision problems.

Seek out hormonal disturbances. If the visual field isn’t a slam dunk, Dr. Golnik advised asking questions related to hormonal dysfunction. Because the pituitary gland controls most of the body’s endocrine functions by secreting various hormones, any physical changes related to hormonal disturbance may help confirm the diagnosis. For example, an elevation of the hormone prolactin can cause galactorrhea (inappropriate lactation) in women and impotence in men. Elevated growth hormone can cause fingers, hands, and feet to grow. “We ask about ring size, shoe size,” Dr. Golnik said. “We ask, ‘Has that been changing?’”

Masqueraders. Of course, any compression on the chiasm or other parts of the visual system can affect vision. So you must consider a diagnosis of any other tumor, an aneurysm, or a demyelinating plaque related to MS. “MRI will rule those out,” Dr. Golnik said (Fig. 9).

MANAGING PITUITARY ADENOMA

If the ophthalmologist discovers the tumor, the next step is referral to a neurosurgeon. Not all pituitary adenomas need to be removed; medication, radia-

tion, and watchful waiting are other management options.

If a tumor isn’t removed and isn’t causing visual problems (tumors smaller than 10 mm typically don’t affect vision), Dr. Golnik repeats the visual field test every six months, as the tumor can grow. “If it doesn’t change for a year or two, I switch to an annual exam.”

If the tumor is removed, the ophthalmologist follows up with postoperative perimetry. If the tumor isn’t completely removed, the patient needs subsequent perimetry at regular intervals.

Visual prognosis. Patients often ask, “Will my vision get better?” If OCT shows a loss of the nerve fiber layer, the answer is no, Dr. Golnik said. But in other cases, vision may return rapidly. For example, tumors that produce prolactin can be shrunk with medications, including bromocriptine and cabergoline. “Vision can improve dramatically in a week or two, from nearly blind to 20/20,” he said.

But timing is everything—the visual outcome depends on how long the tumor has been pressing on the chiasm or optic nerve. Dr. Golnik said, “The main issue for the ophthalmologist is to recognize some of the nonclassic visual field patterns, because prognosis for visual recovery depends on the timeliness of diagnosis.”

MEET THE EXPERTS



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