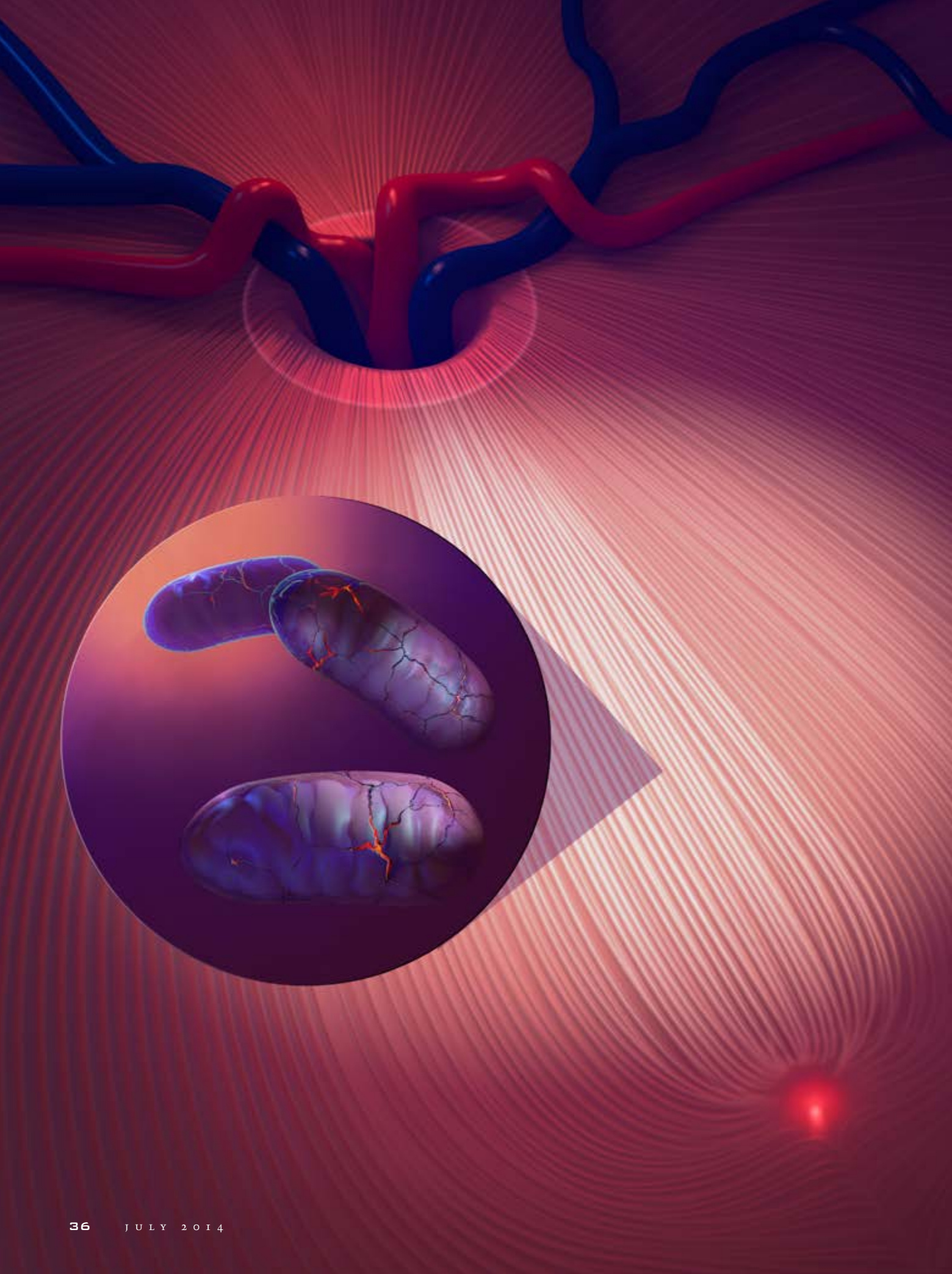


Toxic and Nutritional OPTIC NEUROPATHY

First, Undo Harm

Keeping track of the toxins and nutritional deficiencies that can cause permanent bilateral blindness is no small task. Cued by signature signs and symptoms, however, the clinician can spot many culprits before irrevocable harm is done.

BY ANNIE STUART, CONTRIBUTING WRITER

Characterized by damage to the papillomacular bundle (PMB), acquired optic neuropathy—whether toxic or nutritional in origin—is a problem of largely indeterminate scope. Although ophthalmologists have reported hundreds of cases over the years, gathering incidence data is a challenge without the benefit of large clinical cohorts, said Rick W. Fraunfelder, MD, MBA, at the University of Missouri in Columbia, and with the National Registry of Drug-Induced Ocular Side Effects in Portland, Ore.

In the case of one of the biggest offenders, however, existing statistics may make ophthalmologists sit up and take notice: Of the 9 million new cases of tuberculosis worldwide each year, more than half are treated with ethambutol. About 2 percent of these people—or more than 100,000—suffer serious permanent loss of vision each year.[1]

Types of Acquired Optic Neuropathy

Nutritional. Largely due to a deficiency in vitamin B_{12} and folic acid, nutritional optic neuropathy can result from a wide range of underlying factors, said Andrew G. Lee, MD, at the Methodist Hospital in Houston. These include eating disorders, fad diets, gastric bypass surgery, and hyperemesis gravidarum. In addition, some vegetarians—particularly strict vegans—may be at risk.

Poor diet due to excessive alcohol use may be one of the main contributors to nutritional optic neuropathy in the developed world, said Neil R. Miller, MD, chief of neuro-ophthalmology at the Wilmer Eye Institute. Although alcohol was previously lumped together with tobacco and called tobacco-alcohol amblyopia (TAA), this nomenclature is now controversial. "Most researchers believe that nutrition is the main issue and that cigarettes no longer contain enough cyanide to cause a problem with the optic nerve," said Dr. Miller. He cited a study done years ago in the United Kingdom, during which participants were allowed to drink and smoke at will but were given good nutrition and supplementation. None developed TAA.[2]

Drugs. Of the medications reported to be linked with toxic optic neuropathy (see "Top 10 Toxins"), one class in particular stands out: antibiotics that are used for extended periods, said Alfredo A. Sadun, MD, PhD, at the Doheny Eye Institute in Los Angeles. Many antibiotics don't differentiate between mitochondria and bacteria because the two share the same chemistry, he said. "For example, ethambutol kills tuberculosis by chelating zinc, iron, and copper, which also

ALFRED T. KAMAJIAN

damages the ribosomes of mitochondria," he said.

Vaccines. Dr. Fraunfelder cited a recent finding: a toxic link to every type of vaccine, including influenza; human papillomavirus; hepatitis A and B; and measles, mumps, and rubella (MMR).[3] Vaccination "is associated with a retrobulbar optic neuritis due to a rare type 3 hypersensitivity reaction throughout the body," he said. "The small blood vessels become blocked by immune complexes; this causes an optic neuritis later resulting in optic neuropathy."

Acute toxic exposures. Accidental poisoning can occur with substances such as ethylene glycol, the main ingredient in antifreeze and hydraulic brake fluid, and methanol, a by-product of illicit alcohol production (moonshine) that feels the same as ethanol in the mouth and is also present in some cleaning agents, said Dr. Lee.

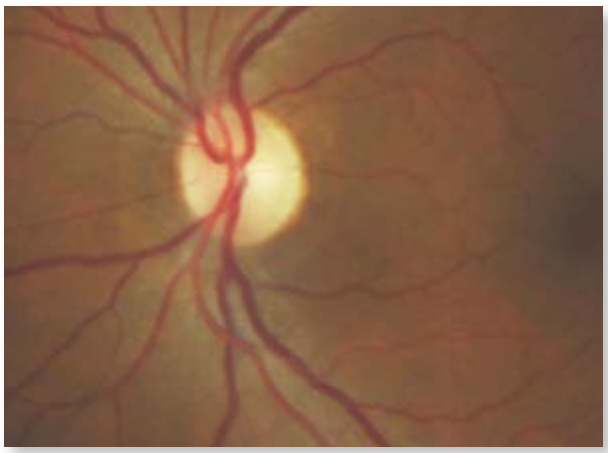
Other types of exposures. "We still have some jobs where heavy metal exposure is a problem, especially in my part of the country, where there are large chemical and petroleum industries," said Dr. Lee. These industries can expose workers to heavy metals such as arsenic, lead, mercury, chromium, and cadmium, he noted, particularly if the worker fails to wear a protective mask.

People exposed to toluene (which is found in gasoline, acrylic paints, varnishes, and glues) can also develop an optic neuropathy, which is almost certainly related to demyelination, said Dr. Miller.

However, said Dr. Sadun, it's exceedingly rare to develop optic neuropathy from these types of exposures.

Underlying Mechanisms of Action

The mitochondrial link. These primary types of acquired optic neuropathy are increasingly called mitochondrial optic neuropathies, due to their common pathophysiology. For instance, toxins can disrupt mitochondrial function, said Dr. Lee, and nutrition-dependent, metabolically active structures can particularly run into trouble because their mitochondria have higher demands.



LATER SIGN. Optic atrophy, seen here, is often not present in the early stages of toxic and nutritional neuropathy.

ANDREW G. LEE, MD

"In all these mitochondrial optic neuropathies, the first thing that goes is part of the optic nerve," said Dr. Sadun. "The PMB is at risk because these fibers are small, unmyelinated, and chock-full of mitochondria." The disease begins with these fine fibers that provide color and the greatest pixel resolution for vision, and it may ultimately cause apoptosis of the retinal ganglion cells with a one-two punch of energy depletion and oxidative stress.[2]

Alternative etiology. In some cases, another toxic reaction may come into play. For instance, said Dr. Miller, "Tumor necrosis factor-alpha inhibitors used for rheumatoid arthritis and psoriatic arthritis can cause toxic effects on the optic nerve that are most likely related to demyelination."

In other cases, damage may result from the direct toxic effect of the metabolite being ingested, said Dr. Lee. For example, major metabolites of methanol are formaldehyde and formic acid. Because toxins such as methanol interfere with oxidative phosphorylation, however, they ultimately also impair the mitochondria, Dr. Sadun added.

Double trouble. It is possible for a single agent to lead to acquired optic neuropathy. "A class of drugs [hydroxyquinolines] used mainly in the Far East and Australia for traveler's diarrhea once caused optic neuropathy and extensive neurologic damage in virtually everyone put on the drug," said Dr. Miller. However, more often, genetics or another factor adds the proverbial insult to injury.

Dr. Sadun witnessed a powerful combination with the Cuban epidemic of optic neuropathy, which took place in 1992 and 1993. "We diagnosed a combination

TOP 10 TOXINS

MEDICATIONS

Ethambutol, rifampin, isoniazid, streptomycin—taken mainly for tuberculosis

Linezolid—taken for bacterial infections, including pneumonia

Chloramphenicol—taken for serious infections not helped by other antibiotics

Isotretinoin—taken for severe acne that fails to respond to other types of treatment

Cyclosporine—a widely used immunosuppressive agent

ACUTE TOXINS

Methanol—a component of moonshine and present in some cleaning products

Ethylene glycol—present in antifreeze and hydraulic brake fluid

of nutritional and toxic optic neuropathy—a deficiency of folic acid and B_{12} combined with exposure to low levels of methanol. Individually, each might have affected a few people, but concurrently, they caused 50,000 people to go blind that year."

Gray areas. In some cases, it isn't possible to tell whether a drug causes the optic neuropathy, or the optic nerve is already compromised by genetics or preexisting disease. Amiodarone, which is prescribed for cardiac arrhythmias, often falls into that gray zone, said Dr. Miller.

The Art of the History

Uncovering an acquired optic neuropathy may take some finesse and focus during history taking. The experts recommend considering the following issues when interviewing patients.

Dose and duration. "Some drugs have a shorter half-life than others, which affects not only how fast optic neuropathy develops but also how long the drug will stay in the system," said Dr. Miller. Patients on ethambutol for months rather than weeks are at higher risk due to an additive effect, said Dr. Fraunfelder. "And the higher the dose, the greater the likelihood of optic neuropathy."

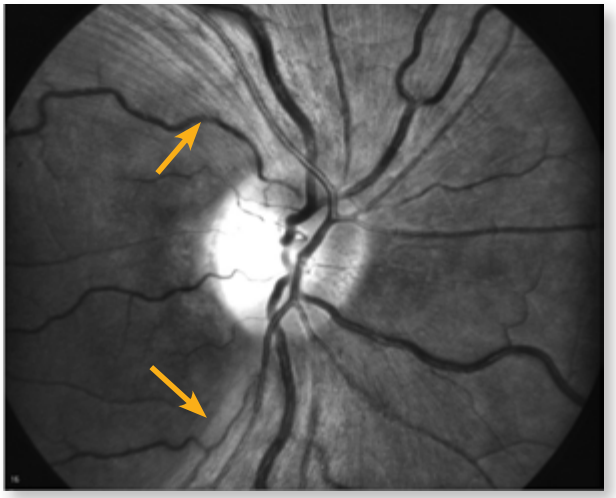
Patient age. Overdose can be a particular problem for older patients, who might weigh less and have poorer creatinine and kidney clearance, said Dr. Sadun. In addition, said Dr. Miller, our mitochondria age along with us, which has a direct impact on recovery. With older patients, it's also important not to jump to conclusions about diagnosis, he said. "Don't do a superficial evaluation because you simply assume an older patient has a cataract or age-related macular degeneration."

Diet deficiencies. Clinicians can get at the nutritional deficiencies linked with alcohol by asking specific questions such as "What did you have for dinner last night? What did you have for lunch? How about the day before?"

In addition, questions that elicit other details—for example, information on mood—may help pinpoint the deficiency. "We once had a patient who developed bilateral nutritional optic neuropathy," said Dr. Miller. "She was very depressed, and her diet consisted solely of drinking a can of Ensure each day."

Ethanol versus methanol. While the impact of ethanol in alcoholic drinks may take a long time to develop, methanol ingestion blinds right away, said Dr. Lee. If you ask patients only about their beer or wine intake, you can miss the occasional moonshine imbiber. "Ask directly, but try not to pigeonhole people," said Dr. Miller. "Anyone could have an optic neuropathy linked with alcohol overuse."

The unusual or provocative. It's important to remember that patients may not give you the whole story because of forgetfulness, embarrassment, or other issues, said Dr. Miller. Gentle probing may be required.



SUBTLE TIP-OFF. Arrows indicate the edges of the wedge-shaped defect that is often indicative of toxic or nutritional optic neuropathy.

In addition, the occasional unusual case may pass through your office, he said. For example, someone who emigrated from another country may have cultural habits unfamiliar to you, such as chewing on the leaves of khat, a flowering plant that is endemic to the Horn of Africa and the Arabian Peninsula and produces euphoria similar to that provided by amphetamines. Khat stimulates production of reactive oxygen species, leading to oxidative damage, said Dr. Miller. It also can disrupt mitochondrial membrane potential and activate the caspase cascade, leading to apoptosis of retinal ganglion cells and optic nerve axonal damage.

The Optimal Workup

Nutritional or toxic optic neuropathies classically cause decreased visual acuity, a central or cecocentral scotoma, and dyschromatopsia. With rare exception, they're bilaterally symmetrical and involve a painless, insidious onset.[4]

In most cases, the recommended workup should include the following.

BCVA. Patients may describe visual loss as a central haze or dark cloud,[3] but objective testing for BCVA can confirm whether vision loss cannot be corrected.

Color vision. A washout of color may occur across the whole spectrum but most often affects the color red, said Dr. Miller. Patients might notice color changes first, and the decrease in color vision may be out of proportion to the degree of central vision loss. "If the vision is poor, the color vision is always poor," he said. "If the vision is not too bad, the color vision may nevertheless be very poor."

To test color, Dr. Miller recommends Hardy-Rand-

JASON CALHOUN, OPHTHALMIC PHOTOGRAPHER, DEPARTMENT OF OPHTHALMOLOGY, MAYO CLINIC JACKSONVILLE

Rittler (HRR) over Ishihara plates. "HRR plates are a little more sensitive and can clearly distinguish a congenital from an acquired color vision loss."

Visual fields. The type of visual field (VF) you perform is important, said Dr. Miller. That's because a central field defect with sparing of the periphery is the hallmark of a nutritional or toxic optic neuropathy. "You might want to do a 10-2 field rather than a 24-2 or 30-2. If the central defect is too small, you may miss it with the usual visual field."

An automated VF that really blows up the center is great for detecting and evaluating early disease, said Dr. Sadun, but you want one large enough to see around the scotoma. "First, you want to categorize it as a bilateral central scotoma," he said, "and then you can go the other direction and microscopically zoom in."

Fling the flashlight? "We're all taught that one of the best tests for optic nerve disease is the swinging flashlight test, otherwise known as a check for a relative afferent pupillary defect," said Dr. Sadun. "It usually doesn't work in cases of toxic optic neuropathy because the disease is bilaterally symmetrical."

Fundus exam. This may also be misleading. "With time, the optic nerve will turn pale, but at first it may appear normal," Dr. Lee said. Dr. Sadun recommends putting in a red-free filter and looking very carefully for a wedge-shaped defect on the temporal side of the retinal nerve fiber layer. "There will be a punching-out of the PMB. It's subtle, but if you see it, you'll know exactly what is going on." (See figure, page 39.)

THREE CASES, THREE QUESTIONS

Diagnosis—and treatment—of optic neuropathy can take detective work, as the following cases illustrate. To comment on these cases, see this article at www.eyenet.org.

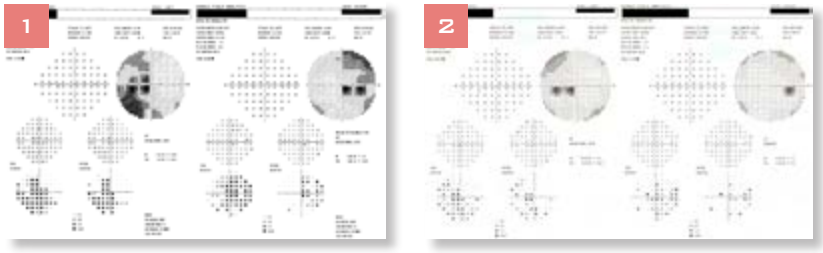
Case #1: MAC Infection

Submitted by Alfredo A. Sadun, MD, PhD

QUESTION: Why didn't the patient get better as soon as the ethambutol was stopped?

A 65-year-old, 150-pound woman is diagnosed with *Mycobacterium avium* complex (MAC) and put on 1,800 mg per day of ethambutol at the beginning of May. Her ophthalmologist follows her for several months, but her exams appear normal. By the middle of October, her colors have become washed out. By November, her best-corrected visual acuity (BCVA) is 20/50 and 20/100. However, the ophthalmologist does not suspect optic neuropathy because there is no sign of optic atrophy.

At six months, the ophthalmologist makes the correct diagnosis and discontinues ethambutol. But a month later, the patient's vision is subjectively worse, with central scotomas and BCVA of 20/200 and 20/400, despite optic nerves that still appear normal. At eight months, when her vision has decreased to counting fingers, the ophthalmologist refers her to a neuro-ophthalmologist, who prescribes vitamins with copper, zinc, and iron. The patient gradually recovers over several more months, progressing from counting fingers at 2 feet to 20/25 vision.



VISUAL FIELDS (1) After taking ethambutol for several months, the patient's vision had decreased and her visual fields showed bilateral cecocentral scotomas with temporal field depression. (2) Three months after the drug was stopped, the patient's visual acuity and visual fields improved.

This patient developed optic neuropathy because her ethambutol dose was 27 mg/kg when it should have been less than 20 mg/kg. Furthermore, her creatinine was elevated to 1.4, so she was effectively overdosed by a factor of 2.

ANSWER: *Although the mitochondria likely recovered in a few days, their retinal ganglion cells (RGCs) needed months to become functional again. There are probably at least two reasons for this: 1) The time it takes for RGCs to move from a dormant to a physiologically normal state and 2) corresponding changes in their myelinated portion that require oligodendrocytes.*

The bottom line: It's important to not give up in cases of mitochondrial disease, especially ethambutol toxicity. Recovery takes time.

Case #2: Acne

Presented by Y. Joyce Liao, MD, PhD, assistant professor of ophthalmology and director of neuro-ophthalmology at Stanford University*

ALFREDO A. SADUN, MD, PHD

Red Amsler grid. If you suspect an optic neuropathy but don't find anything with other tests, said Dr. Sadun, the red Amsler grid may help by simultaneously testing color vision and central vision, providing a nice magnification of the central field.

Lab tests. Blood tests are warranted if you suspect a nutritional deficiency. "Test for serum B_{12} and red blood cell folate, which more accurately determines its status in the system," said Dr. Miller. If a patient's B_{12} is low, but not exceedingly so, Dr. Lee suggests testing for methylmalonic acid and plasma homocysteine; they are metabolic by-products for which B_{12} is a cofactor, so these measurements provide a longer-range picture of B_{12} status.

"If there's a suspicion of heavy metal exposure, you can test hair, blood, and urine," said Dr. Lee. However, if medication is the suspected culprit, the only real test is to stop the drug and watch the results.

Other systemic signs. Acute forms of toxicity will usually be quite obvious, said Dr. Lee, as there will be additional problems such as renal failure or metabolic acidosis. Acute methanol poisoning may cause nausea, vomiting, and loss of consciousness.

Although systemic signs are uncommon, they may occur in certain cases, such as with vaccine toxicity. "When you develop a type 3 sensitivity reaction, this occurs throughout the whole body," said Dr. Fraunfelder. "The patient may experience malaise, fatigue, fevers, joint aches, or peripheral neuropathy, along with the retrobulbar optic neuritis."

QUESTION: Which clues point to an acquired optic neuropathy?

A 19-year-old college student with a history of acne presents with headache and blurry vision. She reports that these symptoms have been present for a week, since a college football game where she was binge drinking. She also notes that her vision "goes black" when she bends over to put on her shoes. For the last week, she has had difficulty falling asleep because of a "funny sound."

Her medical history is significant for a body mass index (BMI) of 35, and she smokes half a pack of cigarettes a day. She is taking oral contraceptive pills and isotretinoin acid for her acne. She has been on doxycycline in the past.

The patient's BCVA is 20/20 in both eyes, and she has no relative afferent pupillary defect. Her intraocular pressure (IOP) is within normal limits, and her anterior segment exam is unremarkable. Her dilated funduscopic exam reveals bilateral severe optic disc edema with blurring of the disc margins, flame-shaped hemorrhages, cotton-wool spots, obscuration of peripapillary retinal vessels, and absent spontaneous venous pulsation. Humphrey VFs reveal enlarged blind spots in both eyes.

ANSWER: *This patient was diagnosed with retinoic acid–induced intracranial hypertension. Symptoms of elevated intracranial pressure include headache, transient visual obscuration, pulsatile tinnitus, diplopia, vision loss, and neck/radicular pain. Idiopathic intracranial hypertension occurs in 19 per 100,000 per year in women between the ages of 20 and 44 who are 20 percent over their ideal weight. Retinoic acid can be a risk factor, even at the doses used to treat acne. Other risk factors include smoking and oral contraceptive use.*

Case #3: Gastric Surgery

Presented by Jacinthe Rouleau, MD, clinical assistant professor of ophthalmology and chief of the neuro-ophthalmology section at the Université de Montréal*

QUESTION: What put this patient at risk for nutritional optic neuropathy?

A 35-year-old female teacher complains of visual loss in both eyes. She states that her vision has gradually declined in both eyes symmetrically over the past four months to the point that she now has difficulty reading.

Her past medical history is significant for morbid obesity (BMI of 45), for which she underwent a gastric bypass (Roux-en-Y) in July 2005. The initial postoperative course was uncomplicated.

She has lost a total of 120 pounds since the bypass surgery. She is a nonsmoker, and she is not currently taking any medications. She has no history of drug or alcohol abuse. Her family history is negative for any eye diseases. Review of systems is notable only for mild lower extremity paresthesias.

On examination, her BCVA is 20/60 in each eye. Her color vision is 7/11 in both eyes when tested with HRR plates. Her pupils are normal, and there is no relative afferent pupillary defect. External exam and ocular motility are normal. Automated VFs show central scotomas in both eyes. Her IOP is 14 mmHg in both eyes, with normal pachymetry. The slit-lamp exam is normal for the anterior segments but reveals mild temporal optic disc pallor in both eyes.

ANSWER: *This patient's risk of nutritional optic neuropathy was elevated once she underwent gastric bypass (GBP) surgery. Numerous nutrient deficiencies can occur after GBP, but those that can potentially result in optic neuropathies include vitamin B_{12}, folate, and thiamine. Although the patient's vitamin B_{12} level came back low at 110 pmol/L, her folate and thiamine levels were normal. The complete blood count showed macrocytic anemia.*

**Cases 2 and 3 were presented at the 2013 Neuro-ophthalmology Subspecialty Day in New Orleans.*

Confirming the Diagnosis

Differential diagnosis. Maculopathy—a macular hole or macular cyst, for example—is most often confused with optic neuropathy, said Dr. Sadun. These conditions can produce a central scotoma and even problems with color, combined with a good-looking optic nerve. What's different? "With maculopathy, there's no wedge-shaped defect of the PMB and no symmetry between the two eyes," he said.

Patients who have oil-drop cataracts may present with gradually progressive visual loss in one or both eyes, said Dr. Miller. "A routine slit-lamp exam may show what appears to be an unimpressive cataract, but retinoscopy in such patients will show a significant opacity."

Genetic history. How do acquired types of optic neuropathy differ from inherited types, such as Leber hereditary optic neuropathy (LHON)? It can be just a matter of severity, said Dr. Fraunfelder. "With LHON, the paleness of the optic disc can be very severe, and blindness can result quickly."

In addition, family history is a tip-off. "To rule out LHON," said Dr. Miller, "you can first look for common mutations, and then sequence the whole mitochondrial genome, if necessary."

Imaging. "If a patient has a color deficit and central visual defect with sparing of the periphery, I feel comfortable not doing imaging," said Dr. Miller. "However, it may be safest to order magnetic resonance imaging to make sure you don't miss that one in a million with a tumor or one in a thousand with multiple sclerosis."

Referral. "When there's no sign of optic atrophy, patients often don't get referred to a neuro-ophthalmologist until things are quite advanced," said Dr. Sadun. There are two reasons for this, he said: 1) Only the fibers of the PMB are involved, and 2) fibers go through a relatively prolonged dormant stage of dysfunction before they die.

Remove toxins. Fortunately, if you stop the offending agent, patients can usually recover some—but not necessarily all—of their vision, said Dr. Fraunfelder. "If you catch it early, that can be very helpful." But proving a drug's culpability by starting, stopping, and reintroducing it to observe outcomes isn't often practical, said Dr. Miller. He added that very few suspected drugs have undergone anything resembling the rigors of Koch's postulate.

Other strategies. In the case of nutritional deficits, good nutrition and supplements—mainly B vitamins—are the simple solution. For methanol-induced toxic reactions, one somewhat counterintuitive treatment is ethanol because it competes for alcohol dehydrogenase, said Dr. Miller. Fomepizole may also be an effective antidote, as it is metabolized by alcohol dehydrogenase.

Last Note: Baseline Exams

If a patient is prescribed a drug that is associated with optic neuropathy, "It's important to get a baseline eye exam," said Dr. Fraunfelder (see "Top 10 Toxins"). "This would include checking visual acuity and color vision, as well as doing a visual field test and dilated fundus exam."

Depending on the drug, you may need to schedule patients for close follow-up, he said. For example, the *Physicians' Desk Reference* recommends seeing patients on ethambutol every month.

Dr. Sadun recommends regular red Amsler grid testing to ensure that these patients don't get into trouble, especially older or younger patients or those with diabetes, chronic renal failure, renal tuberculosis, or alcoholism.[4] ■

1 Sadun AA, Wang MY. *J Neuro-ophthalmol.* 2008;28(4):265-268.

2 Foulds WS et al. *Br J Ophthalmol.* 1974;58(4):386-390.

3 Karussis D, Petrou P. *Autoimmun Rev.* 2014;13(3):215-224.

4 Wang MY, Sadun AA. *J Neuro-ophthalmol.* 2013;33(2):172-178.

MEET THE EXPERTS

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