Ethambutol is the most common and extensively studied cause of optic nerve toxicity. Drug-resistant strains of tuberculosis often necessitate use of this antibiotic. The World Health Organization estimates that there are about 9.2 million new cases of tuberculosis each year (1). About 55% of these patients take ethambutol each year as a treatment for tuberculosis or Mycobacterium avium (1). If we take the conservative estimate that 2% (2) of these individuals will experience significant and irreversible visual loss, then the annual incidence of this serious iatrogenic complication is 100,000.

In this issue of the Journal of Neuro-Ophthalmology, Eun Ji Lee et al (3) report a retrospective analysis of 857 patients who had been given ethambutol in Korea. In this cohort, 89 (10%) complained of visual symptoms. By the authors' entry criteria, only 13 (1.5%) were determined to have optic neuropathy attributable to ethambutol. These 13 patients received average daily doses of 18 mg/kg—well within recommended dosage limits—and lost vision after an average of 7 months, findings that are consistent with previous reports (4). Only one third of the patients recovered vision over a period of approximately 5 months.

With regard to risk factors for the development of the optic neuropathy, the authors found renal dysfunction and daily dose levels to be important. They concluded that the cumulative dose did not significantly contribute to visual loss, but only 3 patients took the medication long enough to reach a $P < 0.05$ significance level.

The authors found that renal function, as demonstrated by glomerular filtration rate, was an important risk factor. This finding is not surprising, given that ethambutol is largely cleared by the kidney. In the personal experience of one of us (AAS), almost every case of ethambutol optic neuropathy involves one or more of the following factors: 1) the patient has been given too large a dose, often because low weight has not been taken into account; 2) the patient has documented poor renal function, and 3) declining renal function with age has not been considered.

Although ethambutol optic neuropathy is the exemplar of toxic optic neuropahties, streptomycin, chloramphenicol, and linezolid produce similar clinical manifestations. The patient develops slowly progressive loss of visual acuity in conjunction with central or cecocentral scotomas, dyschromatopsia, and loss of high spatial frequency contrast sensitivity (5). These psychophysical features are explained by selective damage to the papillomacular bundle. Optical coherence tomography (OCT) confirms axon loss, and fundus examination shows optic disc pallor that is most pronounced on the temporal side. Nutritional disorders such as folic acid or vitamin B$_{12}$ deficiency, and combinations of toxicity and nutritional disorders such as tobacco-alcohol amblyopia and the Cuban epidemic of optic neuropathy produce similar clinical manifestations (6), as do inborn errors of metabolism due to mitochondrial or somatic DNA mutations such as Leber hereditary optic neuropathy (LHON) and autosomal dominant (OPA-1) optic neuropathy (6).
What do these toxic disorders, nutritional deficiencies, and genetic diseases have in common? What can we learn about their pathophysiology by noting common mechanisms? How might understanding this underlying pathophysiology suggest management approaches?

The phenomenon of ethambutol optic neuropathy raises some fundamental questions. Given that ethambutol is designed to impair protein synthesis in prokaryotic cells found in bacteria, why does it particularly injure eucaryotic cells found in humans? Why is the optic nerve so vulnerable? Why are certain patients vulnerable? What accounts for the fact that certain patients recover vision after discontinuation of the drug?

**MITOCHONDRIA ARE THE KEY**

Ethambutol destroys bacteria by chelating the metal ions that are involved in prokaryotic ribosomes. In particular, it inhibits arabinosyl transferase, an important enzyme in mycobacterial cell wall synthesis. Because of the similarity of mammalian mitochondrial DNA and ribosomes to those of bacteria, protein synthesis in mitochondria may be inhibited. Detachment of ribosomes from the rough endoplasmic reticulum and dissociation of polysomes into monosomes that come with prolonged depletion of ATP contribute to reduced protein synthesis. In addition to ethambutol, other agents may cause disrupted oxidative phosphorylation and, not surprisingly, present with similar clinical findings. For example, linezolid inhibits protein synthesis by binding to 23S rRNA of the bacterial 50S ribosomal subunit, thereby inhibiting formation of the 70S initiation complex. Likewise, chloramphenicol inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit.

In the oxidative phosphorylation that occurs in mitochondria, electrons are transferred down a chain of complexes as protons are translocated across the inner membrane to establish an electrochemical gradient. The energy stored in electron transport is coupled to the synthesis of ATP. As a metal chelator, ethambutol can disrupt oxidative phosphorylation and mitochondrial function by interfering with iron-containing complex I and copper-containing complex IV. Other toxins also block oxidative phosphorylation, which inhibits cytochrome c oxidase, and methanol, which leads to formate accumulation and electron transport blockade. The Cuban epidemic of optic neuropathy (CEON) is another acquired mitochondrial dysfunction due to chronic methanol consumption, folic acid and other vitamin deficiency, and exposure to cyanide. LHON is a maternally inherited disease characterized by point mutations in the mitochondrial DNA (mtDNA) affecting complex I in the respiratory chain. Chronic impairment of energy production and accumulation of reactive oxygen species eventually lead to apoptosis and optic nerve degeneration.

Mitochondria provide most of the ATP required by cells. In the process of oxidative phosphorylation, reactive oxygen species are generated as a byproduct. Energy depletion and oxidative stress can lead to mitochondrial damage, resulting in the opening of the mitochondrial permeability transition pore (MPTP) that allows for leakage of cytochrome c, which triggers apoptotic death pathways in the cytosol (Figure 1). Each time an axon undergoes action potential propagation, sodium/potassium pumps must restore the resting membrane potential. This step requires large quantities of ATP. Not surprisingly, mitochondria, the primary source of ATP, accumulate at the nodes of Ranvier and other unmyelinated regions along axons (Fig. 1).

Because axonal transport is highly energy dependent and mitochondria need to be transported from the neuronal somata to the distal synaptic terminals within the short mitochondrial lifespan, retinal ganglion cells (RGCs) with their long axons are particularly vulnerable. Defective mitochondrial function compromises efficient axonal transport, including the transport of the mitochondria themselves. RGC axons of the papillomacular fiber bundle are particularly vulnerable because of their narrow caliber, given that a high surface area to volume ratio favors energy consumption over energy production. In addition, the lack of myelination inside the eye and the fast firing rate upon stimulation make these RGC axons particularly susceptible.

Perhaps as a part of successful compensation in early LHON or ethambutol toxicity, mitochondria accumulate within RGC axons. This accumulation is detectable as axonal swelling by OCT (2,7). Resolution of axonal engorgement upon cessation of ethambutol use may account for the reduction in nerve fiber layer thickness and improvement in the visual field that occurs in some patients. Remyelination of denuded axons may partially explain the late visual recovery observed in some patients with the 14484 LHON mutation or ethambutol toxicity (6). However, axonal loss as reflected by optic disc pallor is an irreversible process.

**PATIENT MANAGEMENT**

With this understanding of the pathophysiology of ethambutol toxicity, what are the appropriate steps in patient management?

The best screening tests for ethambutol toxicity are those that measure the functions of the papillomacular bundle. Good tests include visual acuity, color vision (especially red), contrast sensitivity (especially high spatial frequency), central visual fields (such as Amsler grid or Humphrey Visual field strategy 10-1), and pattern visual
evoked potentials. In particular, the red Amsler grid is an excellent screening test.

Patients with the highest blood levels of ethambutol have the greatest risk for developing visual loss from toxic optic neuropathy. High blood levels of ethambutol are likely in cases in which the patient’s weight was not obtained or was not taken into account or in patients with poor renal function (by age or disease). Children may tolerate higher doses. Therefore, dosage must be properly calculated to avoid untoward ethambutol toxicity (8). Because ethambutol is included in the 2-month initial treatment phase to prevent or delay the emergence of resistance to other antituberculosis drugs, ethambutol should be discontinued once a treatment response has been seen. The treatment regimen should then be tailored according to the susceptibility pattern (8). Because ocular toxicity is rare when ethambutol is taken for only 2–3 months at the recommended dosage, it is appropriate to administer the drug at 15–20 mg/kg per day for 2 months, taking body weight and renal function into account (9). Treatment should be stopped at the onset of any signs or symptoms of ocular toxicity.

It is important to monitor patients regularly for early signs of optic neuropathy and discontinue the drug in a timely fashion. Among those affected with early signs of toxicity, some may recover over a very long time. One reason for a window of reversibility is that mitochondrial impairments do not immediately cause axons to die. The axons first pass through a “sick” period characterized by compensations that include energy depletion, mitochondrial congregation, slowed axonal transport, and axonal swelling (5). Death need not occur unless toxicity is severe.

CONCLUSIONS

How should we change our approach to the use of ethambutol to still effectively treat tuberculosis? Proper management includes identification of patients at risk, adjusting the dose regimen for impaired renal function, body weight, and age, regular monitoring for early signs of ocular toxicity, and patient education. As a biologic phenomenon, ethambutol toxicity reminds us that mitochondria are not merely producers of ATP but also controllers of apoptosis. In nonreplicating tissues such as...
the central nervous system, apoptosis may lead to
degeneration, which probably occurs at a much slower
and less dramatic fashion in Alzheimer and Parkinson
disease. Thus, what we learn about mitochondrial optic
neuropathies is likely to prove invaluable in the prevention
and treatment of far more common neurological conditions.

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