

Toxic/Nutritional Optic Neuropathies: What We Know and What We THINK We Know

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LEARNING OBJECTIVES:

At the conclusion of this talk, the attendee will be able to:

- 1) Differentiate toxic and nutritional optic neuropathies from conditions that mimic them
- 2) Identify the clinical manifestations of toxic and nutritional optic neuropathies
- 3) Understand the controversy surrounding certain presumed toxic optic neuropathies

CME QUESTIONS:

1. All of the following are typical hallmarks of a toxic or nutritional optic neuropathy except:
 - a. Bilateral and symmetric
 - b. Dyschromatopsia
 - c. Altitudinal field loss
 - d. Temporal disc pallor
2. The optic neuropathy that most often is mistaken for a toxic or nutritional optic neuropathy is:
 - a. Leber optic neuropathy
 - b. Acute optic neuritis
 - c. Ischemic optic neuropathy
 - d. Compressive optic neuropathy
3. An optic neuropathy associated with the use of a TNF-alpha inhibitor is most likely due to:
 - a. Ischemia
 - b. Infection
 - c. Demyelination
 - d. Nutritional deficiency

KEY WORDS: toxic optic neuropathy, nutritional optic neuropathy, optic neuropathy, TNF-alpha inhibitor, Leber optic neuropathy, amiodarone, toluene abuse

I. INTRODUCTION AND TWO CASES

Physicians have known for centuries that the anterior visual pathways are vulnerable to damage from nutritional deficiency and chemicals. The resulting disorders share many signs and symptoms, and several appear to have a multifactorial etiology in which both under-nutrition and toxicity play a role.

Although certain optic neuropathies have an obvious toxic or nutritional etiology (eg, ethambutol, methanol), the toxic or nutritional basis of others is merely presumptive, and the attribution may ultimately prove false. Consider the following two cases:

Case #1:

In 1978, a 31-year-old otherwise healthy man sued the United States government, claiming that shortly after receiving the "swine flu" vaccine in September of 1976, he lost vision in both eyes. An examination at this time revealed acuity of CF OU with dense central scotomas and some peripheral field constriction. Both optic discs were said to be pale. A diagnosis of "toxic" optic neuropathy due to the influenza vaccine was made, and the patient's case was actually published in the literature under the title "Bilateral Optic Nerve Atrophy and Blindness Following Swine

Influenza Vaccination."¹ I was a witness for the defense and testified that it was likely that the patient had Leber hereditary optic neuropathy (LHON). It was subsequently shown in court that the patient's visual loss had begun several weeks before the vaccine was available to the public (mass vaccinations were not begun until October of 1976). Following publication in 1988 of Doug Wallace's seminal paper on the genetics of LHON,² I contacted the patient's attorney and recommended that the patient undergo genetic testing. As expected, he had the 11778 (Wallace) mutation.

Case #2

A 28-year-old woman was evaluated at Johns Hopkins because of progressive decreased vision in both eyes that she indicated had occurred shortly after gastric bypass surgery for morbid obesity. A diagnosis of presumed nutritional deficiency-related optic neuropathy had been made but vitamin assays had shown no deficiency. When examined by me, the patient indicated that her visual loss had occurred rather rapidly and that she had experienced some mild ocular discomfort at onset. She had visual acuity of 20/100 OD and 20/200 OS. Color vision was markedly diminished. The patient had bilateral small central scotomas. There was no RAPD. The temporal aspects of both optic discs were pale. A CT scan (MRI was not available at this time) was unremarkable, and a lumbar puncture revealed no abnormalities in the CSF. The patient was discharged on vitamin supplements; however, 3 months later, she developed numbness and tingling of her extremities, and a repeat LP showed elevated protein and six oligoclonal bands in the CSF. A diagnosis of multiple sclerosis was made and subsequently supported several years later by MRI. In the meantime, the patient was treated with systemic steroids with improvement in her vision to 20/40 OU.

These cases illustrate the pitfalls of diagnosing toxic or nutritional optic neuropathies. Conversely, it also is likely that a few of the optic neuropathies now considered idiopathic or ascribed to some other etiology, actually result from toxicity or nutritional deficiency. Nevertheless, there are cases in which it is clear that there is a toxic and/or nutritional etiology.

II. SUBACUTE MYELO-OPTIC NEUROPATHY (SMON): "KOCH'S POSTULATES (VAR)" CONFIRM A TOXIC OPTIC NEUROPATHY

The primary issue in patients suspected of having a toxic optic neuropathy is whether or not they were exposed to a substance that has been proved to damage the optic nerve by the same route of exposure. Visual loss may occur from either acute or chronic intoxication depending upon the agent, but there should not be a long interval between the cessation of the exposure and the onset of symptoms. The patient must have symptoms and signs that are compatible with a toxic optic neuropathy and typical of those in other patients proved to have suffered loss of vision from the same agent. Of course, the symptoms cannot have preceded the exposure.

The response of patients to re-challenge is helpful in evaluating the validity of presumed intoxications and in helping to establish the cause of the patient's optic neuropathy. If a patient who has recovered vision following cessation of exposure to a drug or chemical loses vision again when re-exposed, the recurrent loss of vision tends to verify the neurotoxic nature of the agent and the toxic etiology of the visual loss. Epidemiologic data, especially those showing correlation of changing disease incidence when and where specific drugs or chemicals are introduced or withdrawn, can also prove quite useful. A perfect example of these issues is the optic neuropathy that occurred in patients treated with halogenated hydroxyquinolines for various gastrointestinal disorders producing severe diarrhea.

The halogenated hydroxyquinolines are amebacidal drugs. One of these (iodochlorhydroxyquin) was promoted in some parts of the world for preventing or treating traveler's

diarrhea and chronic diarrheas. Between 1956 and 1970, an epidemic of 10,000 cases of a new neurologic syndrome--subacute myelo-optic neuropathy (SMON)--occurred in Japan. Although the epidemic was recognized promptly and a multidisciplinary search for the etiologic agent was begun, it was not until 1970 that careful retrospective case-control and cohort studies implicated a halogenated hydroxyquinoline, iodochlorhydroxyquin, as the agent responsible. Tsubaki et al.³ observed neurologic symptoms in 35.4% of patients taking this drug for more than 14 days and also found that of 171 patients examined with evidence of SMON, 166 (96%) had taken the drug prior to the onset of neurologic symptoms. Nakae et al.⁴ conducted a nationwide survey and collected 1839 cases of SMON of which 75% had received iodochlorhydroxyquin. In the meantime, in September of 1970, the Japanese government removed all halogenated hydroxyquinolines from the market, and the epidemic ended precipitously.⁵ In addition to the Japanese experience, numerous authors from other countries reported SMON or isolated optic atrophy (with diiodohydroxyquin) associated with ingestion of halogenated hydroxyquinolines including Great Britain,⁶⁻⁹ Australia,¹⁰⁻¹² Switzerland,¹³ Sweden,¹⁴⁻¹⁷ Denmark,¹⁸ the Netherlands,¹⁹ and the United States.²⁰⁻²⁴ Of most significance is that not only do several reports demonstrate the potential for reversal of the visual loss once the drug is stopped but also recurrence of visual loss when the drug was restarted. For example, Etheridge and Stewart²¹ reported a young child who was treated with diiodohydroxyquin in a dose of 3200 mg daily for 2 years. The patient developed visual loss in the range of 20/200 bilaterally with optic atrophy 1 month after an increase in the dosage to 3600 mg/day. When the dose was lowered, the patient's vision improved and then worsened when the dose was raised. Billson et al.¹⁰ reported an 18-year-old woman with ulcerative colitis who developed progressive blurred vision in both eyes after 9 months of treatment with Clioquinol at a dosage level of 2000 mg/day. On initial examination, the patient had visual acuity of 20/200 in each eye with bilateral cecocentral scotomas and normal fundi. Clioquinol was stopped, and the patient's vision gradually improved to 20/80 in the right eye and 20/40 in the left eye with diminution in the size of the scotomas. About 1 year later, the patient was restarted on Clioquinol because of exacerbation of her colitis. Two days after restarting the drug at a dosage of 2000 mg/day, she patient noted severe loss of vision and presented with visual acuity of 20/600 in the right eye and 20/200 in the left eye, large, bilateral cecocentral scotomas, and bilateral, severe optic atrophy. The drug was immediately stopped, and within 2 days there was dramatic improvement in the patient's visual acuity to 20/200 in the right eye and 20/120 in the left eye. Within the next 2 weeks, visual acuity had improved and stabilized at 20/120 in the right eye and 20/40 in the left eye (this case was reported in more detail by Reich and Billson¹²). The "SMON Story" is one of the best examples of proof of a clear-cut toxic optic neuropathy. Not all such cases are as clear. Take the case of amiodarone.

III. AMIODARONE-ASSOCIATED "TOXIC" OPTIC NEUROPATHY

Amiodarone is a benzofuran derivative that is primarily used to treat atrial or ventricular tachy-arrhythmias that are unresponsive to other anti-arrhythmic agents.²⁵ Amiodarone's therapeutic mechanism of action is related to its ability to prolong the duration of action potentials and the refractory period in cardiac-conducting tissues. The most common ocular side effect is the formation of verticillate, pigmented, corneal epithelial deposits that eventually occur in most patients (70–100%) treated with the drug. The amount of corneal epithelial deposits observed in a given patient, as well as the incidence of these deposits in a group of patients, is related to the dose of the drug and the duration of treatment. With discontinuation of the drug, the deposits resolve over several months as amiodarone has a long half-life of up to 100 days. Other ocular side effects from amiodarone include anterior subcapsular lens opacities, multiple chalazia, and keratitis sicca. Fortunately, these ocular side effects rarely cause significant visual impairment and do not constitute a reason for discontinuing the drug.²⁵

Amiodarone sometimes is associated with an optic neuropathy that has many characteristics similar to nonarteritic anterior ischemic optic neuropathy (NAION). Indeed, in 1982, Chew et al.²⁶ were the first to mention a case of what was thought to be NAION in a patient taking amiodarone, although they gave no details about the case as the point of their paper was to describe the corneal findings. Subsequently, Gittinger and Asdourian²⁷ reported this association in two patients treated with therapeutic doses of amiodarone. They described a 45-year-old man who had unilateral, hemorrhagic disc edema noted on a routine examination 8 months after starting treatment with amiodarone. He was asymptomatic and had normal visual acuity, color vision, and visual fields. His disc edema resolved 1 month later despite continued treatment with the drug. The other patient was a 61-year-old man who complained of hazy vision in his right eye two months after starting treatment with amiodarone. He had a visual acuity of 20/25 OU, a right RAPD and hemorrhagic disc edema in the right eye. Several days later, he developed hemorrhagic disc edema in the left eye. Three months later, he still had bilateral, hemorrhagic disc edema and his dosage of amiodarone was reduced. Five months after his visual loss, he had a visual acuity of 20/20 OU, an inferior arcuate defect in the right visual field, disc edema OD, and resolution of his disc edema OS.

Feiner et al.²⁸ subsequently described 13 patients who developed an optic neuropathy during treatment with amiodarone. The amiodarone dosage ranged from 200 to 600 mg/day and the time interval between initiation of amiodarone therapy and the manifestation of optic neuropathy ranged from 1–72 months. Three patients had no visual symptoms and disc edema was noted on a routine examination. The remaining 10 patients complained of blurry or decreased vision and presented with visual acuities ranging from 20/20 to 20/400. Nine patients had visual field deficits including arcuate scotomas, altitudinal deficits, centrocecal scotomas, enlarged blind spot, and visual field constriction. Among the 13 patients, 12 had disc edema and five had bilateral ocular involvement. Three patients had recovery of vision after amiodarone was discontinued, whereas patients had a final visual acuity of 20/100 or worse.

Several other investigators have described patients that developed an optic neuropathy while being treated with amiodarone.²⁹⁻⁴⁰ In 1997, a 50-year-old man who became legally blind from a bilateral optic neuropathy that developed 6 weeks after the initiation of amiodarone therapy was awarded a \$20 million judgment in a lawsuit against the pharmaceutical company that sold the drug at that time.⁴¹

The nature of the association of optic neuropathy and amiodarone treatment is controversial. Many of the patients described in the above reports developed an optic neuropathy that is indistinguishable from nonarteritic anterior ischemic optic neuropathy (NAION). Feiner et al.²⁸ noted that the 1.79% incidence of optic neuropathy among patients treated with amiodarone at the Mayo Clinic was significantly higher than the 0.3% incidence of ischemic optic neuropathy in the general population 50 years of age or older in Olmsted County, Minnesota. However, patients treated with amiodarone often have severe vascular disease and probably have a higher risk of developing anterior ischemic optic neuropathy compared with the general population.

The lawsuit described above stimulated Macaluso et al.⁴² to try to establish criteria with which to distinguish "amiodarone-associated optic neuropathy" from NAION (one of the authors was a witness at the trial!). These investigators reviewed data from 73 patients who developed an optic neuropathy while taking amiodarone. They noted that patients with amiodarone-induced optic neuropathy tend to have insidious bilateral visual loss and protracted, bilateral simultaneous disc edema that resolves several months after the drug is discontinued. These findings were echoed by Purvin et al.^{42a} In contrast, patients with typical NAION tend to have acute unilateral visual loss and

disc swelling that resolves several weeks after visual loss. Despite these distinctions, there is certainly overlap in the clinical spectrum of these two entities.

Adding to the controversy surrounding amiodarone is a study by Joel Mindel and co-workers.⁴³ These investigators assessed 1669 subjects receiving either weight-determined doses of closed-label amiodarone (n=837) or placebo (n=832) in a prospective double-masked fashion. Closed-label amiodarone subjects were followed, unless death occurred, for a minimum of 27 months. Median follow-up in survivors was 45.5 months. The end point was removal from the study because of bilateral visual loss. In fact, NO SUBJECT was removed from the study because of bilateral vision loss. The authors concluded that "at the doses commonly used clinically, bilateral vision loss from amiodarone toxic optic neuropathy occurs infrequently, if at all."

Despite the findings of Mindel et al., it is important to remember the dictum of William Cowper, the great English poet: "Absence of proof is not proof of absence".⁴⁴ Some patients in this study may have experienced a unilateral or bilateral optic neuropathy caused by amiodarone but either not recognized by the patient because it was too subtle or attributed to something else, such as developing cataracts.

The mechanism of amiodarone-induced optic neuropathy--assuming that it exists--may be related to the fact that amiodarone binds phospholipids within lysosomes and forms a complex that is not degradable by phospholipase enzymes^{25,45} The amiodarone-phospholipid complex accumulates within lysosomes and forms cytoplasmic lamellar inclusions. These lamellar inclusions have been observed in the cytoplasm of many tissues including corneal epithelial, stromal, and endothelial cells; lens epithelium; conjunctival epithelium; extraocular muscle fibers; scleral cells; uvea; blood vessel endothelial cells; retinal ganglion cells; retinal pigment epithelium; and optic nerve axons. Indeed, these inclusions are likely responsible for the corneal and lens deposits noted above.

The available data are insufficient to make firm recommendations regarding a screening protocol for patients treated with amiodarone. Macaluso et al.⁴² recommended obtaining a baseline examination on all patients prior to starting amiodarone treatment and repeating the examination every 6 months during treatment. I believe that all patients taking amiodarone should be told of the potential for visual issues and the need to contact their ophthalmologist immediately should they experience any visual sensory disturbance. Amiodarone may be a life-saving treatment, and the occurrence of an optic neuropathy is therefore not an absolute contraindication to further treatment; however, in patients who have an optic neuropathy while on amiodarone, discontinuation of amiodarone and treatment with an alternative drug should be considered. A superb overview of this issue was published by Murphy and Murphy.⁴⁶

IV. TOXIC OPTIC NEUROPATHY ASSOCIATED WITH TNF-ALPHA INHIBITORS

TNF- α is a multidimensional cytokine with effects on cellular metabolism, antiviral activities, coagulation processes, growth regulation of cells and insulin response.⁴⁷ It was named based on its ability to stimulate necrosis of malignant tumors but soon was found to be an important mediator of cutaneous inflammation. It is activated mainly by T-lymphocytes and macrophages during acute inflammation.

TNF- α is known to play a crucial role in the pathogenesis of many chronic inflammatory diseases. Elevated levels of TNF- α have been demonstrated in Crohn disease (CD), psoriasis (Ps), psoriatic arthritis (PsA) and rheumatoid arthritis (RA), suggesting a role for TNF- α in their pathogenesis⁴⁸⁻⁵¹ and providing a rationale for the treatment of these diseases with drugs that inhibit it.

TNF- α blockers have demonstrated efficacy in large, randomized controlled clinical trials, either as monotherapy or in combination with other anti-inflammatory or disease modifying anti-rheumatic drugs (DMARDs).^{52,53} At the time this syllabus was written, five TNF- α inhibitors were available for clinical use: infliximab, adalimumab, etanercept, golimumab and certolizumab pegol. All of these drugs block the biologic effects of TNF- α although there are some differences in their structure, pharmacokinetics and mechanisms of action (Figure 1).⁵⁴

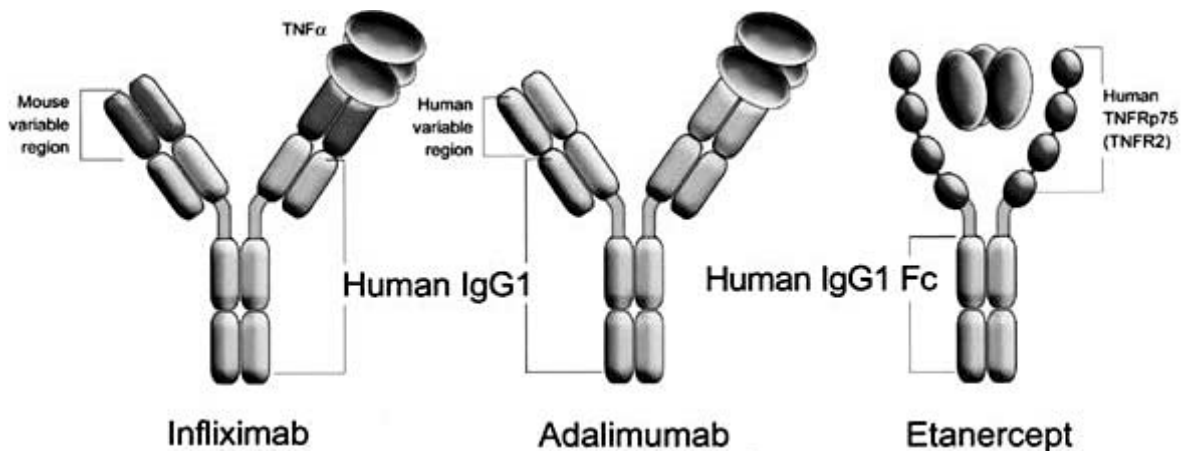


Figure 1. Anti-TNF molecules bind to and neutralize the activity of TNF α . Infliximab and adalimumab are monoclonal antibodies. Infliximab is a mouse/human chimera that joins the variable regions of a mouse antibody to the constant region of human IgG1, and adalimumab is a human IgG1 antibody. Etanercept is a dimeric fusion protein that joins the human p75 TNF receptor to the Fc domain of human IgG1. Reprinted from Shukla R, Vender RB. Pharmacology of TNF inhibitors. In Weinberg JM, Buchholz R (eds) . TNF-alpha Inhibitors. Birkhäuser Verlag. Switzerland, 2006; pp. 23-44.

The efficacy and safety profile of the TNF- α inhibitors can be considered, in general, as a class effect. Nevertheless, some differences exist among the five agents. Infliximab is a chimeric human/murine IgG1 monoclonal antibody (mAb) directed against TNF- α , that has been approved in combination with methotrexate (MTX) for the treatment of RA. The ATTRACT and ASPIRE studies confirmed that infliximab (3 mg/Kg intravenously at weeks 0-, 2- and 6- and 8-weekly thereafter) plus MTX provided greater clinical and functional benefits than treatment with MTX alone for the treatment of RA.⁵⁵ Infliximab alone (5 mg/Kg) also has been approved for the treatment of Ps, PsA, AS, CD and ulcerative colitis refractory to conventional drugs.^{53,56,57} Furthermore, infliximab is considered the treatment of choice for fistulizing CD.⁵⁷ Colombel et al. reported that infliximab plus azathioprine was the most effective treatment, for moderate-to-severe CD.⁵⁸ Episodic therapy with infliximab on relapse of CD is possible but is less efficacious and frequently is associated with problems resulting from the formation of antibodies to infliximab. If treatment is episodic, maintenance therapy with immunosuppression (azathioprine, MTX) is mandatory.⁵⁹

Adalimumab is a fully recombinant human IgG1 anti-TNF- α -specific mAb approved for the treatment of Ps, PsA, RA, AS and CD.^{53,60} The PREMIER study demonstrated that adalimumab (40 mg subcutaneously every other week) plus MTX was significantly superior to either MTX alone or adalimumab alone in improving signs and symptoms and inhibiting

radiographic progression of early, aggressive RA.^{60,61} In addition, Colombel et al. demonstrated that continuous treatment with adalimumab was more effective than induction dosing followed by re-initiation of adalimumab with clinical deterioration for maintenance of clinical remission, improved quality of life outcomes, reduced flares and a decrease in the number of surgeries and risk of hospitalization in patients with active CD.⁶²

Golimumab is a human gamma-1 immunoglobulin-k anti-TNF- α monoclonal antibody and is administered as a 50-mg subcutaneous injection once a month.⁵⁶ Golimumab was approved for use with MTX in adults with moderate to severe RA, and with or without MTX or other DMARDs in adults with active PsA or active AS. Boyce et al. confirmed the efficacy of golimumab.⁶³

Certolizumab pegol differs from the other anti-TNF- α agents by its structure, composed of the Fab antigen-binding domain of a humanized monoclonal anti-TNF- α antibody combined with polyethylene glycol to increase its half-life in the body.⁶⁴ Certolizumab pegol in combination with MTX is indicated for the treatment of moderate to severe, active RA, and it also has been recommended for the treatment of CD.^{65,66}

Etanercept is not a monoclonal antibody, but a fusion protein that acts as a 'decoy receptor' for TNF- α and acts competitively to inhibit the binding of TNF- α to its cell surface receptor.⁵³ It has been approved for the treatment of Ps, PsA, AS and juvenile RA.⁵³

The differences in the mechanism of action of the TNF- α inhibitors are reflected by the variable response rate observed in patients with CD who respond well to infliximab and adalimumab but not to etanercept. In addition, patients who fail to tolerate one TNF- α inhibitor can be switched to another TNF- α inhibitor if allowed by the nature of the adverse event.

Although TNF- α inhibitors are generally well tolerated, all have potential adverse effects.^{67,68} The most frequent adverse effects are: 1) infusion reactions with infliximab, 2) injection-site reactions to subcutaneously administered drugs, and 3) mild infusion reactions (i.e., headache, itch, urticaria, nausea) and cutaneous injection-site reactions (i.e., local erythema and swelling) that usually subside within 24 hours and that can be treated with premedication with anti-histaminic drugs and, when needed, with glucocorticoids.⁵³ Severe infusion reactions (i.e., angioedema and shock) have been reported in patients under infliximab therapy. As infliximab is a chimeric human/mouse anti-TNF- α antibody, it may induce the synthesis of neutralizing antibodies that could reduce the efficacy of the drug. MTX usually is co-administered to control both the rheumatic disease and the development of neutralizing antibodies.⁵³ Despite its fully human sequence, the production of antibodies to adalimumab also has been reported, and this may reduce the efficacy of the drug and induce the development of adverse drug reactions and exanthema.⁶⁷ Malignancies (i.e., lymphomas), autoimmune diseases and demyelinating diseases (see below) have been reported in patients taking TNF- α inhibitors. Finally, TNF- α inhibitors may cause reactivation of latent tuberculosis and increase the overall risk of opportunistic infections such as those caused by *Histoplasma capsulatum*, *Coccidioides immitis*, *Listeria monocytogenes*, and invasive fungi such as *Aspergillus* and *Candida* species.⁶⁷

There have been infrequent reports of central nervous system (CNS) demyelinating disorders during treatment with anti-TNF- α agents. Several of these cases have been temporally related to anti-TNF therapy and have resolved when treatment was withdrawn.⁶⁸ Mohan et al.⁶⁹ reviewed the occurrence of neurologic events suggestive of demyelination during anti-TNF- α therapy for various inflammatory arthritides. The Adverse Events Reporting System

of the Food and Drug Administration (FDA) was queried following a report of a patient with refractory RA who developed confusion and difficulty with walking after receiving etanercept for 4 months. 19 patients with similar neurologic events were identified from the FDA database, 17 following etanercept administration and two following infliximab administration for inflammatory arthritis. All neurologic events were related temporally to anti-TNF therapy, with partial or complete resolution on discontinuation. One patient exhibited a positive re-challenge phenomenon. The authors concluded that further surveillance and that studies were required to better define risk factors for and frequency of adverse events and their relationship to anti-TNF therapies. Until more long-term safety data are available, rheumatologists advise that consideration be given to avoiding anti-TNF therapy in patients with pre-existing multiple sclerosis and to discontinuing anti-TNF therapy immediately when new neurologic signs and symptoms occur, pending an appropriate evaluation.^{68,69}

As far as optic neuropathies associated with anti-TNF- α treatment are concerned, it would appear that they are not "toxic" in the normal sense of the word, but rather due to demyelination stimulated by the agents. Be that as it may, there is some evidence that patients taking TNF- α inhibitors are at increased risk from a unilateral or bilateral optic neuropathy that may be a form of optic neuritis. Winthrop et al.⁷⁰ performed a retrospective, population-based cohort study in which they identified new users of anti-TNF- α therapy (etanercept, infliximab, or adalimumab) or non-biologic DMARDs during 2000–2007 from several data sources. Within this cohort, they used validated algorithms to identify cases of optic neuropathy occurring after onset of new drug exposure. They then calculated and compared the incidence rates between exposure groups. They identified 61,227 eligible inflammatory disease patients with either new anti-TNF- α or new nonbiologic DMARD use. Among this cohort, they found three cases of optic neuropathy among anti-TNF- α new users, occurring a median of 123 days (range, 37–221 days) after the start of therapy. The crude incidence rate of optic neuropathy across all disease indications among this cohort was 10.4 (95% CI 3.3–32.2) cases per 100,000 person-years. In the cohort with current or past anti-TNF- α or DMARD use, they identified a total of six optic neuropathy cases: three among anti-TNF- α users and three among DMARD users. Crude ON rates were similar between the two groups: 4.5 (95% CI 1.4–13.8) and 5.4 (95% CI 1.7–16.6) per 100,000 person-years, respectively. The authors therefore concluded that new-onset optic neuropathy/optic neuritis is rare among those who begin treatment with TNF- α inhibitors and occurs with similar frequency among those with nonbiologic DMARD exposure. This validity of this conclusion was questioned by Eggenberger,⁷¹ who emphasized a number of potential inaccuracies in the way the diagnosis of "optic neuritis" was made and pointed out that there was, in fact, biological plausibility with respect to a causal association between TNF- α inhibitors and the development of demyelinating events including true optic neuritis. Several years ago, I was retained by Pfizer to assess cases reported to the company of possible optic nerve damage in patients using etanercept (Enbrel®). Although there were several cases of true optic neuropathy, many of the histories and examination results were so vague that one could not determine what was going on. Even worse, some cases clearly either were not examples of optic nerve damage at all and others were not consistent with a demyelinating event. Nevertheless, there are in the literature several case reports that suggest a potential for the development of a unilateral or bilateral optic neuropathy in patients taking TNF- α inhibitors, some of which were associated with other manifestations of multiple sclerosis. In particular, Li et al.⁷² reported a case of optic neuritis and multiple sclerosis and identified 21 cases of unilateral or bilateral anterior or retrobulbar optic neuritis (or at least optic neuropathies) associated with TNF- α inhibition (see Table 1 in Li et al.⁷²). Among these cases, 36% with available MRI results had evidence of other demyelinating lesions in the CNS. I agree with those who say that such agents should be used with caution--if at all--in patients with multiple sclerosis and, as in the case of patients beginning treatment with amiodarone, patients about to be placed on one of the TNF- α inhibitors should be told about the

possibility of visual loss and told to contact their ophthalmologist immediately should they experience any visual sensory or neurologic symptoms or signs.

V. TOXIC/NUTRITIONAL OPTIC NEUROPATHIES FROM SUBSTANCE ABUSE: YOUR PATIENT MAY NOT/WILL NOT TELL YOU!

A. Alcohol-Related Optic Neuropathy

Perhaps the most common toxic or deficiency optic neuropathy in the United States is that once termed "tobacco-alcohol amblyopia." Optic neuropathy related purely to tobacco abuse appears no longer to exist, and many individuals believe this relates to "safer tobacco" without contaminants, but alcohol-related optic neuropathy continues to appear on a regular basis. Most of the patients who develop alcohol-related optic neuropathy are males, and symptoms begin at a later age than that associated with the majority of cases of optic neuritis. Patients with presumed alcohol-related optic neuropathy do not show spontaneous improvement but may improve to a variable degree once alcohol consumption is halted, dietary habits are improved, and treatment with vitamin supplement is begun (see below).

Quigley et al.⁷³ studied the number and distribution of human optic nerve axons in a patient with presumed alcohol optic neuropathy. The patient was a 51-year-old man who died of lung carcinoma. He had abused alcohol throughout his adult life and suffered from cirrhosis, pancreatitis, systemic hypertension, and diabetes mellitus. The patient's left eye developed uncontrolled open-angle glaucoma and lost all vision. Intraocular pressures in the patient's right eye averaged 18 mm Hg, but visual acuity in that eye varied from 20/50 to 20/100 with a full peripheral field and a central scotoma. Although the cup/disc ratio of the right optic disc was only 0.4, there was significant temporal disc pallor. Quigley and co-workers found that the right optic nerve contained fewer than one-half the normal number of fibers. There was a striking loss of the temporal quadrant of nerve fibers; however, in the other three quadrants, nerve fiber loss was also significant, averaging about 40%. Thus, the selective damage to the temporal quadrant--presumably the papillomacular bundle--was accompanied by a diffuse loss of axons in the other quadrants as well.

The etiology of this bilateral, primarily retrobulbar, optic neuropathy is controversial. At the heart of the controversy is one issue: Is there a direct toxic effect of alcohol on the optic nerve or is this condition, in reality, a nutritional disorder related to a deficiency of vitamin B12, folic acid, thiamine, or some other substance. One of the major problems in deciphering the precise cause of the amblyopia is that patients who develop the disorder often are generally malnourished. Thus, the separation of critical factors is often impossible. Nevertheless, several investigators have attempted to isolate the factors involved in the production of this disorder (?these disorders). Alcohol is known to reduce the absorption of vitamin B12⁷⁴ and this, as well as simple dietary insufficiency of vitamin B12, folic acid, thiamine, etc. may, individually or together, be responsible; however, controlled studies have yet to be performed. Carroll⁷⁵ studied 25 patients with presumed "tobacco-alcohol amblyopia." The patients were allowed to drink and smoke in their usual manner, providing that they ate a nutritious diet supplemented with B vitamins and folic acid. All of the patients recovered vision completely or almost completely. In addition, several investigators^{76,77} have found low levels of red blood cell folate but normal levels of vitamin B12 in patients with presumed alcohol-related optic neuropathy and documented improvement in visual parameters when such patients are treated with folate alone. The importance of assessing red blood cell folate rather than serum folate in patients with suspected alcohol-related optic neuropathy cannot be overemphasized.

B. Toluene (Methylbenzene)

Toluene, or methylbenzene, a colorless, sweet, and pungent-smelling liquid naturally present in crude oil, is produced in enormous amounts worldwide.⁷⁸ Although some toluene remains in gasoline and motor fuel products, much of the toluene content of crude oil is extracted in refineries. This toluene then is sold for use in the production of chemicals, like benzene, and in the formulation of paints, graphic pigments, adhesives, lacquers, paint strippers, printing ink, spot removers, cosmetics, perfumes, and antifreeze.⁷⁹ In addition to these traditional uses, toluene may be inhaled to achieve instantaneous intoxication. This is done by "sniffing" (i.e., inhaling vapors from an open container), "bagging" (i.e., inhaling more concentrated vapors from a closed container), or "huffing" (i.e., breathing through a solvent-soaked cloth).⁸⁰ Cheap, legal, and readily available, products with substantial toluene content, typically glues or paint thinners, offer optimal substances of abuse for those without access to other illicit drugs. Consequently, toluene abuse is most prevalent in adolescents, particularly those of lower socioeconomic backgrounds.⁷⁸ Lifetime prevalence rates of inhalant abuse ranging from 8 to 25% among high school students.⁸⁰ In addition, more than half of those reporting a history of inhalant use have done so multiple times, and 77% state they have abused inhalants for more than 1 year.⁸¹

The tremendous morbidity and mortality associated with this behavior are often underappreciated. From 1987 to 1996 in Virginia alone, there were 39 inhalant-related deaths (two died abusing pure toluene or products containing mostly toluene and several more died abusing products that contained toluene as a key ingredient).⁸² Chronic toluene abuse can cause irreversible renal, hepatic, cardiac, and pulmonary toxicity;^{78,83} however, the magnitude and range of toluene's CNS effects eclipse its peripheral toxicity profile. Coordination and gait impairment occur in chronic toluene abusers⁷⁸ as may slurred speech, intention tremors, rigidity, spasticity, and hyperreflexia.⁸⁴⁻⁸⁶ Ocular motor dysfunction, including pendular nystagmus, ocular flutter, opsoclonus, and bilateral internuclear ophthalmoplegia also have been described.^{84,87-89} Correspondingly, both cerebellar atrophy and cerebellar tract damage as well as diffuse white matter changes have been documented by neuroimaging in these patients.^{84,85,90,91}

As far as optic nerve damage is concerned, Keane⁸⁸ reported the case of a 20-year-old man who gave a 3-year history of inhaling a spray paint mixture containing metallic copper, toluene, and xylene as solvents and isobutane propane and methylene chloride as propellants. The patient developed progressive ataxia and bilateral visual loss with acuities of 4/200 in each eye, dyschromatopsia, moderately constricted visual fields, sluggish pupillary responses to direct light stimulation, and normal fundi. Following cessation of paint sniffing, the patient's neurologic symptoms slowly subsided, and within 2 months, his visual acuity had improved to 20/30- in each eye, his color vision was mildly impaired as tested with pseudoisochromatic color plates, and his visual fields were full. Although his fundi were said to be normal, pattern-reversal visual evoked responses showed prolonged, although improved, latencies. It seems likely that this case represents a true toxic reaction to toluene, particularly as a similar case of reversible optic neuropathy was reported after industrial exposure to vinyl benzene (styrene).⁸⁹ Other patients have had permanent visual loss. Ehyai and Freemon⁹⁰ reported the case of a 27-year-old man who developed progressive ataxia, sensorineural hearing loss, and bilateral optic atrophy over a 5-year period during which he sniffed glue extensively. At the time his visual loss began, the optic discs were observed to be normal in appearance, indicating a retrobulbar process. Other investigators have reported similar cases.^{84, 95-100}

A more recent article by Gupta et al.⁹¹ emphasized the problem making the diagnosis of a toluene-induced optic neuropathy in the setting of other white-matter disease. These authors described two patients with bilateral optic neuropathies. One, a 28-year-old man, also had

progressive ataxia, weakness, and numbness. He underwent an extensive evaluation that culminated in a brain biopsy that showed demyelination and reactive gliosis. Despite years of denial of drug abuse or toxin exposure, the patient finally admitted to recreational inhalation of spray paint for 13 years. The second patient was a painter who had been exposed to paint products, some of which contained toluene or toluene products, for 27 years. Gupta et al. emphasized that the optic neuropathy caused by toluene exposure is characterized by a slow progressive decline in visual acuity ranging from 20/20 to 4/200 with associated diminished color vision in most patients.^{88,92,93} The initial optic disc appearance usually is normal, but patients gradually develop optic atrophy. Visual fields reveal enlargement of the blind spot and central depression.^{92,93} Treatment with vitamins, steroids, gabapentin, or cessation of toluene exposure results in an improvement in visual acuity and symptoms in about half the patients;^{92,94} however, in general, the visual prognosis is poor.

Evidence suggests that, despite important inconsistencies in the literature, toluene exerts an effect on the mesocorticolimbic system that likely involves dopaminergic (especially, D2), cholinergic, GABAergic, and serotonergic neurons, but how and why it damages neurons and astrocytes, leading to significant white-matter (including optic nerve) damage remains unknown; however, it is clear that chronic toluene intake results in widespread demyelination including demyelination of the optic nerves.^{95,96}

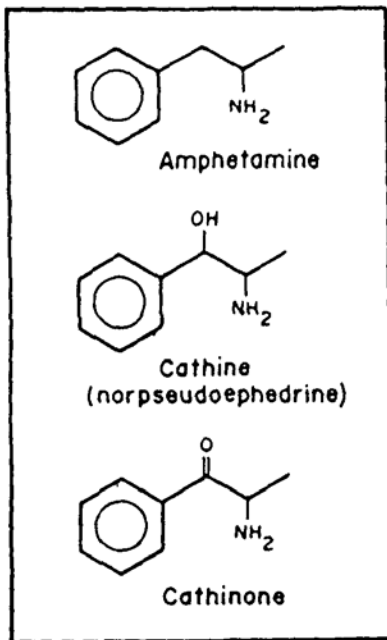
C. Native Medicines

Catha edulis Forsk, or khat, is a member of the family Gesneriaceae and has been grown for centuries in parts of eastern Africa and southern parts of the Arabian peninsula.⁹⁷ The fleshy, pinnate leaves are chewed by millions of inhabitants of these countries for the drug's ability to produce euphoria, combat fatigue, and as part of social gatherings (Figure 2).



Figure 2. *Catha edulis* (Khat). The leaves of this plant are chewed to produce euphoria and to combat fatigue.

Khat grows at 3000 to 6000 feet (900-1800 m) above sea level and reaches a height of 20 feet (6 m). It can survive drought, and the leaves can be harvested throughout the year. The plant is seedless, and this may explain its limited geographical distribution. Extensive thin-layer and gas-liquid chromatographic analyses of the fresh leaves of the khat plant have isolated three major compounds: cathine (i.e., norpseudoephedrine or phenylpropanolamine), cathinone (i.e., α -aminopropiophenone), and norephedrine.⁹⁷⁻⁹⁹ Both cathine and cathinone are similar in structure to amphetamine (Figure 3).⁹⁷



Cathine was identified in 1930, and for a long time it was believed to be the only active stimulant in khat. Cathinone was isolated in 1975. It is a ketone congener of cathine, and it is now believed that it is the main active principle responsible for khat's stimulant properties.

Khat induces amphetamine-like sympathomimetic and central stimulant effects in users. The pharmacological effects include mydriasis, tachycardia, extra systoles, hypertension, conjunctival congestion, headaches, and increased respiration. Anorexia and insomnia also are common in habitual users.

Several cases of bilateral optic neuropathy have been reported in individuals in whom Khat abuse was the only potential cause. For example, Baird¹⁰⁰ reported the occurrence of a bilateral anterior optic neuropathy in two khat abusers in Somalia in whom visual function improved and optic disc swelling resolved upon withdrawal of khat. Roper¹⁰¹ reported the development of

a bilateral optic neuropathy in two patients who, although they were longstanding users of the leaves of *Catha edulis*, had chewed larger quantities than usual over a short period of time. Both patients had bilaterally decreased visual acuity, central scotomas, sluggish pupillary responses without a relative afferent defect, loss of retinal nerve fibers in the papillomacular bundle, and optic atrophy. One of the patients also had some retinal pigmentary abnormalities. Neither individual had any other risk factors for the development of a nutritional, toxic, or metabolic optic neuropathy. Thus, Roper concluded that the cause of the optic neuropathies in both patients was related to Khat abuse. Although one might assume that it would be rare for someone living in the Western hemisphere to see patients who experience a toxic reaction to a drug not normally present in that area, due to increasing air transportation and the loosening of customs restrictions, it is now readily available in the Western Countries, mainly used by immigrants from khat-growing areas. In addition, the fact that the stimulants in khat have a structure similar to that of amphetamine suggests that abusers of similar drugs (eg, methylenedioxymethamphetamine aka MDMA aka ecstasy) could present with similar findings, as it is known that MDMA stimulates the production of reactive oxygen species, leading to oxidative damage.¹⁰² MDMA also promotes disruption of mitochondrial membrane potential and activates the caspase cascade, leading to apoptosis.¹⁰³ Ingestion of MDMA also may increase the extracellular concentration of glutamate,¹⁰⁴ and this may mimic impaired activity of the EAAT1 glutamate transporter, recently linked to mtDNA mutations of LHON.¹⁰⁵ The resulting exocytotoxic damage to both optic nerves and retinal ganglion cells. Indeed, Cardaioli et al.¹⁰⁶ reported the case of a 17-year-old boy who experienced acute, bilateral, asymmetric, painless visual loss after two consecutive treatments with telithromycin and simultaneous abuse of cocaine and ecstasy. On examination, the patient had visual acuity of 20/100 OD and 20/200 OS, with bilaterally reduced color vision, bilateral cecocentral scotomas, no relative afferent pupillary defect, and optic discs with telangiectatic vessels. The patient was subsequently found to harbor the 14484 Leber mutation. It was suspected that the use of cocaine and ecstasy may have rendered the patient susceptible to the effects of the mutation, resulting in his becoming symptomatic.

VI. CLINICAL CHARACTERISTICS OF TOXIC AND NUTRITIONAL OPTIC NEUROPATHIES

Individuals of all ages, races, places, and economic strata are vulnerable to the toxic and nutritional deficiency optic neuropathies. Certain groups are at higher risk because they are under treatment with drugs, because of occupational exposure, or because of habits such as smoking and drinking. Nutritional deficiency optic neuropathy is more likely to occur in the economically disadvantaged and during times of war and famine. The value of taking a thorough history, including dietary intake, exposure to drugs, use of tobacco, and social and occupational background is obvious.

The symptoms and signs of nutritional and toxic optic neuropathy are similar and resemble those of most of the other optic neuropathies, primarily those that occur bilaterally and simultaneously. No single characteristic or combination of characteristics is pathognomonic.

Toxic and nutritional optic neuropathies are not painful. Thus, one should inquire carefully about this symptom since the presence of pain would suggest some other diagnosis.

Dyschromatopsia is present early and may be the initial symptom in observant patients. Some patients notice that certain colors, such as red, are no longer as bright and vivid as previously. Others experience a general loss of color perception.

Patients with nutritional or toxic optic neuropathies often initially notice a blur, fog or cloud at the point of fixation, following which the visual acuity progressively declines. The rate of decline can be quite rapid. Although vision can decrease to any level, total blindness or vision limited to light perception is unusual in cases of nutritional optic neuropathy, even if the patient is neglected. With the exception of methanol, which typically produces complete or nearly complete blindness, visual loss less than 20/400 is unusual in the toxic optic neuropathies. Bilaterality is the rule, although in the early stages, one eye may be affected before the other becomes symptomatic. Profound loss of vision in one eye with completely normal findings in the other eye should cast doubt on the diagnosis of a toxic or nutritional optic neuropathy.

Patients with toxic or nutritional optic neuropathies typically have central or centrocecal scotomas with sparing of the peripheral visual field. Some perimetrists claimed that centrocecal scotomas with "nuclei" between fixation and the physiologic blind spot were the hallmark of toxic optic neuropathy, especially the variety blamed on tobacco.¹⁰⁷ There are many who doubt this, and most authorities now recognize that both central and centrocecal scotomas may be encountered in either disorder.¹⁰⁸⁻¹¹¹ Some patients have a central scotoma in one eye and a centrocecal scotoma in the fellow eye. Peripheral constriction and altitudinal visual field loss are rare.

Because of the symmetric and bilateral visual impairment in toxic and nutritional optic neuropathies, a relative afferent pupillary defect is not a common finding in affected patients. When the patient is blind or nearly so--e.g., as a consequence of methanol poisoning--the pupillary light response will be absent or weak and the pupils will be dilated. Otherwise the pupils are likely to have relatively normal responses to light and near stimulation.

In the early stages of toxic and nutritional deficiency optic neuropathy, the disc may be normal, slightly hyperemic, or swollen. It thus is no surprise that these optic neuropathies may mimic--or be mimicked by--LHON.¹¹² Optic atrophy develops after a variable interval.

VII. DIFFERENTIAL DIAGNOSIS

When an individual complains of bilateral visual loss that refraction cannot correct, and has an otherwise normal examination, there are many diagnostic possibilities in addition to the toxic

and nutritional optic neuropathies. Certain maculopathies can present in this guise.¹¹³⁻¹¹⁹ With time, the fundus will show abnormalities, but until then, fluorescein angiography, multifocal electroretinography, pattern electroretinography, autofluorescence, or a combination of these techniques may be the only means of establishing the diagnosis of a retinal process.¹¹⁹ Ganzfeld electroretinography may be helpful when there is a diffuse retinal process, but if the process is focal, involving less than 25% of the retina, it will not reveal the defect. It also should be emphasized that an abnormal ERG often will result in an abnormal VEP. Thus, in most instances of unexplained visual loss, it is best to obtain an ERG when ordering a VEP. If both tests show abnormal results, the electrophysiologist and you will have to decide if the changes in the VEP are primary and responsible for the patient's visual loss or if the retina is responsible and the VEP changes merely reflect abnormal retinal function causing abnormal transmission from the retina to the optic nerve.

One should be alert to the possibility of a conversion disorder or malingering in cases of bilateral visual loss. The absence of optic atrophy is an important clue when the visual loss is long standing. In the acute phase, the characteristics of the visual field defects may help the clinician recognize that the loss of vision is nonorganic. The visual field defects in the toxic and nutritional optic neuropathies are typically central or centrocecal. Such defects are exceptional in patients with a conversion reaction or who are malingering.¹²⁰ In conversion reaction and malingering, the visual fields are usually constricted and may show spiraling or have a tubular configuration.

Autosomal-dominantly inherited (Kjer) and mitochondria-inherited (Leber) optic neuropathies can be confused with nutritional optic neuropathy if no other family members are known to be affected. The confusion is most likely to occur in patients who are first evaluated late in their course. Autosomal-dominant optic neuropathy progresses much more slowly than the nutritional and toxic optic neuropathies, and optic atrophy is an early finding.¹²¹ In Leber optic neuropathy, the onset of visual loss not infrequently is symmetric or nearly so, and this disorder must therefore be considered in any patient in whom a toxic or nutritional optic neuropathy is thought to be present.^{112,122-125} Appropriate testing for mitochondrial DNA mutations may be required in some cases.

It can be tragic to mistake a compressive or infiltrative lesion of the optic chiasm for nutritional or toxic optic neuropathy. There are few instances in which one should be so confident of the diagnosis of toxic or nutritional optic neuropathy that neuroimaging is omitted. Centrocecal scotomas and the bitemporal visual field defects of chiasmal disease resemble each other, and there are many examples of bilateral central and even centrocecal scotomas from tumors.¹²⁶⁻¹³⁵

If a demyelinating, inflammatory, or infectious optic neuritis begins simultaneously in both eyes, there may be confusion with the toxic and nutritional optic neuropathies. The visual field defects are similar, but there is pain in about 90% of cases of optic neuritis. In some cases, magnetic resonance (MR) imaging will indicate the nature of the lesion. In others, however, it may be necessary to examine the cerebrospinal fluid, perform specific tests for syphilis, sarcoidosis, or systemic vasculitis, and perform a complete neurologic examination.

VIII. EVALUATION

In most cases, analysis of the symptoms and signs obtained from a detailed history and physical examination will establish the diagnosis of a toxic or nutritional optic neuropathy. As stated above, it is prudent to obtain neuroimaging unless one is absolutely confident of the diagnosis. MR imaging before and after intravenous injection of gadolinium-diethylenetriamine-pentaacetic acid (gadolinium-DTPA) with special attention to the optic nerves and optic chiasm, is the optimum

investigation in most cases. A vitamin B₁₂ level should be determined to identify pernicious anemia, and red blood cell folate levels provide one marker of general nutritional status.^{76,77} In addition, in patients with a low or low-normal serum vitamin B₁₂ level, assays for homocysteine and methylmalonic acid also may be appropriate.¹³⁶

When a specific intoxicant is suspected, one should try to identify the toxin or its metabolites in the patient's tissues or fluids. The advice of a toxicologist is invaluable in such instances. In cases of suspected intoxication, one should attempt to evaluate or obtain information about other persons who have had similar exposure. The resulting information has potential public health implications and can help to validate the toxicity of chemicals not previously recognized as dangerous to the human optic nerve.

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CME ANSWERS

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2. a
3. c