Abstract
Vitamin deficiencies of B$_{12}$ (cobalamin) and B9 (folic acid) are common causes of nutritional optic neuropathy. We present a unique case report of a patient with normal B$_{12}$ levels and deficient folic acid levels. Folic acid deficiency, along with excessive alcohol and tobacco use, resulted in decreased visual acuities and paracentral visual fields defects. A 57-year-old male experienced a bilateral, insidious, and painless decrease in vision over a two-month period and was found to have tobacco-alcohol amblyopia (TAA), an optic neuropathy related to nutritional deficiency in combination with excessive tobacco use and/or alcohol (ethanol) consumption. With proper supplementation, he experienced significant improvement in vision, but with a devastating outcome leading to his death. This case report illustrates a unique case of folic acid deficiency contributing to TAA, as vitamin B$_{12}$ deficiency is more frequently associated with TAA.

Introduction
Toxic and nutritional optic neuropathies are frequently discussed together due to their similar features and the difficulty in distinguishing between their relative contributions in most cases. Tobacco-alcohol amblyopia (TAA) is an example, which is typically the result of heavy ethanol and/or tobacco use along with a nutritional deficiency. The combination of these insults produces an insidious optic neuropathy.

Case Report
A 57-year-old Caucasian male presented for an ocular health examination complaining of painless, progressive loss of vision in both eyes for approximately two months. He did not remember having an eye examination in the past. Initial best-corrected visual acuities were 6/18- (20/60-) OD and 6/30- (20/100-) OS with a refractive error of +1.50-1.00 x 080 OD and +1.25-0.50 x 090 OS. Anterior segment examination was found to be unremarkable with normal ocular tensions in each eye. Fundus examination revealed round cup-to-disc ratios of 0.40 OD and 0.50 OS without notching, obvious pallor or optic nerve head edema. The maculae had no apparent pathology and peripheral retinas were examined to be flat and intact OU.

The patient admitted he had been smoking two packs of cigarettes per day for at least twenty years and also drinking heavily since his son’s death approximately seven years ago, typically a pint of vodka per day. His diet consisted of one canned, processed meal per day, either chili or beef stew, and he had lost approximately thirty-six pounds over a period of two to three months. Automated visual fields were ordered and the patient was to be monitored as soon as possible for a return visit. Blood work was also ordered, including: fasting blood glucose (95 mg/dl; reference range: 70-99), antinuclear antibody (ANA) (Negative; reference range: <1:40), angiotensinconverting enzyme (ACE) (59 U/L; reference range: 9-67), hemoglobin A1c (5.1%; reference range: 4.2-5.8), Westergren sedimentation rate (3 mm/hr; reference range: 0-15), all of which were within normal limits.

The patient returned for a follow-up visit three weeks later with no change in subjective complaints. His color vision was 4/7 OD and 1/7 OS when tested with Ishihara’s test plates. His best-corrected visual acuities were 6/30 (20/100) OD and 6/30 (20/100) OS with no significant change in refraction. Visual field testing revealed two moderate paracentral defects OD and three dense paracentral defects OS (Fig. 1). Funduscopic photographs were taken and mild temporal pallor was noted OS (Fig. 2). The following additional labs were ordered: complete blood count (CBC), folic acid, and vitamin B$_{12}$. Blood labs for both red blood cell count (4.06 Mil/cmm; reference range: 4.7-6.1) and folic acid (1.39 ng/mL; reference range: >=3) were low, while his vitamin B$_{12}$ (442 pg/ml; reference range: 211-911) blood serum level was normal. A nutrition consult was ordered, along with a psychology consult as the patient admitted to depression since his son’s death.

The nutritionist gave the patient advice on eating a balanced diet and further advised to take a daily multivitamin and vitamin B$_1$ (thiamin) supplement. It is believed that B$_1$ was emphasized because of the patient’s alcoholism, malnutrition and optic nerve disease. Vitamin B1 is involved in many cellular processes, but greatly assists the circulatory and nervous systems of the body (Table 1).
The patient returned for a follow-up appointment three months later. The patient reported eating more balanced meals regularly and taking a multivitamin and folic acid supplement that his primary care physician recommended. Best-corrected visual acuities drastically improved to 6/12-2 (20/40-2) OD and 6/12- (20/40-) OS with similar refraction. Color vision tested again with Ishihara and was: 3/12 OD and 2/12 OS.

Unfortunately, we were unable to order pertinent imaging as the patient passed away less than two months later due to a hemorrhagic stroke. Further details are unknown, and all attempts of inquiry found no answers.

**Discussion**

Typical complaints for TAA are a slow, progressive, painless vision loss over several months. The decreased acuity is bilateral, though frequently asymmetric. Color vision deficit is classic, with a blue-yellow defect preceding a characteristic red-green defect. Cecocentral or paracentral visual field defects are often observed. These central scotomas are small and relative. Other differential diagnoses included: compressive optic neuropathy, LHON, or medication-induced optic neuropathy.

Compressive optic neuropathy is an important differential diagnosis and should have been ruled out immediately. Neuroimaging must be obtained when optic nerve involvement is suspected in cases of vision loss with lack of evident fundus findings. Imaging would have been ordered with our patient if the nutrition and vitamin supplementation did not show vision improvement. This imaging would have ruled out any type of tumor, lesion, or other compression that may come into contact with the optic nerve.

Leber’s Hereditary Optic Neuropathy (LHON) has a similar presentation as described for TAA above, but the central scotomas are large and absolute. It also shares in that the optic disc may be normal or slightly hyperemic with small disc hemorrhages in the early stages. Temporal pallor of the optic disc appears later, followed by optic atrophy. It has been suggested that TAA and LHON share a common pathophysiological process. The retinal nerve fibers of the papillomacular bundle are affected in TAA, along with LHON and numerous other optic neuropathies, which accounts for the cecocentral/paracentral visual field defects. It appears that these smaller caliber axons are more susceptible to energy depletion or insult by reactive oxygen species (ROS) than other fibers of the optic nerve.

Medication-induced optic neuropathy is another option for this patient’s diagnosis. Our patient’s only medications consisted of the low-grade, over-the-counter, anti-inflammatory medications.

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**Figure 1.** Visual field testing revealed two moderate paracentral defects OD and three dense paracentral defects OS.
naproxen and ibuprofen. The patient denied abusing these medications, which provide a very low chance of causing an optic neuropathy. Broad and rare adverse reactions have occurred with ibuprofen. They have been documented as visual disturbances, visual field defects, or diplopia. In 2006, Gamulescu et al.6 documented a case where optic neuritis may have been caused by 400 mg of ibuprofen three times a day for three weeks. No other optic nerve disease has been associated to either naproxen or ibuprofen.

Optic neuropathy has been observed with isolated tobacco use or in non-smoking alcoholics with or without an accompanying nutritional deficiency. Funduscopic presentation is slightly different depending on the etiology. Asymmetric optic nerve involvement and disturbances of lens accommodation are more characteristic of tobacco amblyopia, whereas alcoholics present with retrobulbar forms.4 Tobacco contains numerous toxic compounds, including ROS and cyanide, which reduce mitochondrial respiratory activity, damage mitochondrial DNA, and induce alterations of mitochondrial morphology.2,3 Ethanol also disrupts antioxidant mechanisms.4

The exact mechanism by which folic acid deficiency leads to optic neuropathy is unidentified; however, it is thought that the increased vascular supply to the optic nerve bundle increases the potential for toxicity.7 Folic acid is involved in the detoxification of formate, a substance that if allowed to accumulate, can block mitochondrial oxidative phosphorylation by inhibiting cytochrome oxidase.8 A study by Martin-Amat et al.9 found that intravenous injection of toxic levels of formate into rhesus monkeys led to optic disc edema with intra-axonal swelling and mitochondrial disruption.

Poisoning from methanol or wood grain alcohol, is another example of formate intoxication resulting in optic neuropathy, but is much more severe. Methanol is metabolized into formate in the liver and then inhibits the cytochrome oxidase complex of the mitochondrial respiratory chain. Vision loss occurs 12-24 hours after ingestion, with optic nerve hyperemia and edema. Optic atrophy results approximately two months later.10

It has been proposed that the origin of the optic neuropathy observed in TAA is mitochondrial dysfunction. Mitochondria are a major source of ATP and mitochondrial axonal transport requires ATP. The mitochondria are transported to the ends of the axons to aid in synaptic transmission. It is likely that energy depletion could result in impaired axonal transport and, therefore, impaired synaptic transmission.2,4 Depletion of energy alone does not explain why other cell types are not affected. The retinal pigment epithelium cells and the photoreceptors, both energy-dependent, are not affected in TAA. Other studies have suggested that free radical damage by ROS likely plays a role.2 It has been proposed that free radicals adjust the control of apoptosis, leading to greater retinal ganglion cell death.4 Due to their small size, the fibers that compose the papillomacular bundle have the lowest volume (energy source) to surface area (energy demand) ratio. They also have a thinner myelin sheath in the post-laminar optic nerve and a more rapid rate of firing than the other fibers, resulting in the highest energy requirement for proper function.2 The fact that the fibers of the prelamellar portion of papillomacular bundle are both unmyelinated and highly concentrated with mitochondria, greatly increase their vulnerability.11

Vitamin B$_{12}$ deficiency is most commonly discussed in nutritional optic neuropathy. However, we present a case with normal B$_{12}$ levels and deficient folic acid levels. Folic acid deficiency, along with excessive alcohol and tobacco use, resulted in TAA. In this case, folic acid deficiency apparently played a major role, as the patient had been abusing alcohol and tobacco for at least six years. Most cases of nutritional optic neuropathy where folic acid is believed to play a role have occurred in conjunction with alcohol abuse, which is the likely primary etiology of the poor nutrition.8

Vitamin deficiencies, especially of the B-group have been implicated as a contributing factor in TAA.4 Lack of Vitamin B$_{12}$ is the only proven deficiency to cause optic neuropathy. The deficit is rarely due to a deficient diet, but more often poor absorption.
Smoking is known to impair vitamin B₁₂ absorption.³ Alcoholics often have a poor diet, and B₁₂ deficiency is exacerbated by poor absorption in the presence of ethanol.³

Vitamin B₁, B₂ (riboflavin), and folic acid are also associated, but not solely responsible with nutritional optic neuropathies, as are the sulfur containing amino acids, homocysteine and methionine. These substances are required for mitochondrial oxidative phosphorylation. Therefore, a deficiency would result in blockage of the electron transport chain, resulting in energy depletion and free radical formation.³

An inverse relationship exists between the duration of the nutritional deficiency and the neurological recovery that follows supplementation. Visual recovery will not occur once axonal loss is complete.¹² Therefore, early diagnosis and treatment are essential in averting permanent vision loss in TAA, which is unfortunately often delayed due to the insidious onset typical of TAA.⁴ Prompt laboratory testing and neuroimaging followed by the appropriate supplementation is crucial. Previous case reports have shown that early initiation of parenteral vitamin B₁₂ can improve visual acuity and dyschromatopsia within just weeks.¹³

The resolution of the CEON was dramatic after the administration of B-complex vitamins.³ In one study, twenty patients were examined prior to and subsequently three months following treatment. The average visual acuity recovered from 6/120 (20/400) to 6/15 (20/50) and average color vision improved from 2/8 to 7/8 using American Optical Color test plates.¹⁵ The CEON is an example of multifactorial pathogenesis for optic neuropathy consisting of both toxic and nutritional factors.¹

Hsu et al⁸ discussed a unique case where folic acid deficiency appeared to be the sole cause of optic neuropathy. The subject had been receiving monthly injections of B₁₂ for three years prior to the onset for megaloblastic anemia and admitted to smoking thirty cigarettes and drinking one glass of brandy per day for at least ten years. Laboratory testing revealed low serum folic acid levels and normal vitamin B₁₂ levels. Vision recovered to 6/6 (20/20) after fifteen months of treatment that included daily folic acid supplementation and eating an overall more balanced diet. During those fifteen months, the subject did not change her smoking or drinking habits. Additionally, a study by Yukawa et al¹⁶ showed that in 343 neurological patients with a variety of diseases (cerebrovascular, Alzheimer’s, Parkinson’s, multiple sclerosis, neurodegenerative, various neuropathies, Pick’s and others) with neurological symptoms also had folate deficiency. These symptoms were frequently decreased after only two months of folate supplementation. A symptom was considered improved when any one clinical sign or symptom was ameliorated.

Van Guelpen and associates¹⁷ conducted a rather large prospective, nested case-referent study providing evidence suggesting a protective role for folic acid, possibly in addition to its effects on homocysteine status, in hemorrhagic stroke. Our patient’s homocysteine levels were not known; however, the treatment to improve homocysteine levels is B₁₂ and folic acid, which was prescribed. The treatment was considered effective as his visual acuities were improved. With the drastic outcome of a hemorrhagic stroke, it is questioned whether the treatment was a little too late, illustrating the importance of prompt diagnosis and treatment in cases of TAA. It would have been more advantageous if the patient had an ocular health examination two months earlier when his symptoms first manifested.

**Conclusion**

TAA is a relatively rare but important differential diagnosis when a patient presents with insidious vision loss without explanatory ocular findings. Prompt diagnosis with subsequent supplementation of deficient B-group vitamins and discontinuation of the use of toxic substances prove critical in the prevention of irreversible vision loss with TAA. We present a unique case demonstrating how a deficiency in folic acid contributed to TAA, which is significant because vitamin B₁₂ deficiency is more frequently associated with TAA. This case shows how significant improvement in visual acuities can occur with proper supplementation; however, our patient had a devastating outcome nonetheless.

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**References**