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Neurologic Manifestations of Systemic Disease (A Wilkins, Section Editor)

Treatment and Outcomes in Nutritional Optic Neuropathy

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Abstract

Purpose of review Nutritional optic neuropathy is a potential cause of severe visual loss; however, appropriate and timely management can result in excellent visual outcomes. The purpose of this review is to outline our current understanding of the treatment and outcomes for nutritional optic neuropathy.

Recent findings Current understanding of nutritional optic neuropathy has been greatly aided by some well-reported and investigated epidemics of the condition, most notably the Cuban epidemic optic neuropathy of the early 1990s. More recently, there is an emerging literature surrounding nutritional deficiencies that can occur in patients who have undergone bariatric surgery. There also continues to be a stream of case reports in the literature that add to our understanding. Nutritional optic neuropathy has a great deal of overlap with toxic optic neuropathies and hereditary optic neuropathies and should not be thought of in isolation from these conditions.

Summary The mainstay of treatment for nutritional optic neuropathy involves identifying and replacing deficient nutrients as well as identifying and eliminating contributory toxins. It is also important to identify contributory genetic factors and to consider the broader social, economic and societal factors which may contribute.

Introduction

Nutritional optic neuropathy is an uncommon, although potentially under-recognised, cause of visual loss. It is mainly seen in the developing world, although specific examples occur worldwide, particularly related to alcoholism. Through history, however, there have been epidemics of nutritional optic neuropathy affecting certain populations, and these have greatly contributed to our current understanding of the condition. These have included Strachan's syndrome in Jamaican sugar cane workers in the 1880s, a similar peripheral and optic neuropathy in prisoners of the Japanese during World War II, tropical amblyopia in Nigerians, Cuban epidemic optic neuropathy, and Tanzanian epidemic optic neuropathy [1–5]. The most studied of these was the 1992/1993 Cuban epidemic, which affected over 50,000 Cubans (0.5% of the population) [6, 7]. This was striking, perhaps, as it occurred in a population where there was free access to a generally high-quality health service and overt malnutrition was not prevalent [7]. More recently, there is an emerging group of patients in the Western world who are at risk of developing nutritional optic neuropathy: patients who have undergone bariatric surgery [8•].

The typical presentation of nutritional optic neuropathy is with subacute, bilateral, fairly symmetrical, painless visual loss [4, 9]. There is early and profound dyschromatopsia, loss of contrast sensitivity (especially at high frequencies), and there may be either a central or centrocaecal visual field defect. Reduction of the afferent light reflex may be noted. Optic disc changes include disc swelling, loss of the papillomacular bundle, mild hyperaemia, haemorrhage, and later atrophy (see Fig. 1) [10, 11]. These clinical characteristics are similar to those seen in inherited optic neuropathies (Leber hereditary optic neuropathy and autosomal dominant optic atrophy) and toxic optic neuropathies. It is likely that disruption of mitochondrial oxidative phosphorylation is central to the pathogenesis of these optic neuropathies, and together, they have been termed mitochondrial optic neuropathies [11, 12]. Toxic and nutritional insults can also precipitate the onset of Leber hereditary optic neuropathy [13–15]. In toxic-nutritional optic neuropathies, nutritional deficiencies lower the threshold of the optic nerve to withstand otherwise tolerable toxic insults [6, 16]. It has been argued that the term 'tobacco-alcohol amblyopia' should no longer be used, since the condition is an optic neuropathy (not an amblyopia), which is primarily due to nutritional deficiency, since alcoholics often have a poor diet with contributing toxic influences usually from cyanide in tobacco smoke [17, 18•].

The epidemic nutritional optic neuropathies were often in association with peripheral neuropathy. The original description of Strachan's syndrome included a painful peripheral neuropathy with sensory ataxia, whilst in the Cuban epidemic, approximately 50% were affected by a peripheral sensory neuropathy and less commonly features of myelopathy [1, 6].

Methods of literature search

We searched MEDLINE from 1946 to June 2018 using 'Optic nerve diseases' (MeSH term) AND ['nutrition disorders' (MeSH term) OR 'nutritional status' (MeSH term)]. Reference lists of articles were reviewed. Further searches were directed by topics identified in the initial literature search and were made using MEDLINE or PUBMED.

Treatment

The mainstay of treatment in nutritional optic neuropathy is to eliminate any toxic influences and correct nutritional deficiencies. It is therefore important firstly to identify which nutrients are deficient and which toxins, if applicable, are at play. The possibility of a hereditary optic neuropathy should also be considered and eliminated with genetic testing if there is an appropriate clinical presentation or family history.

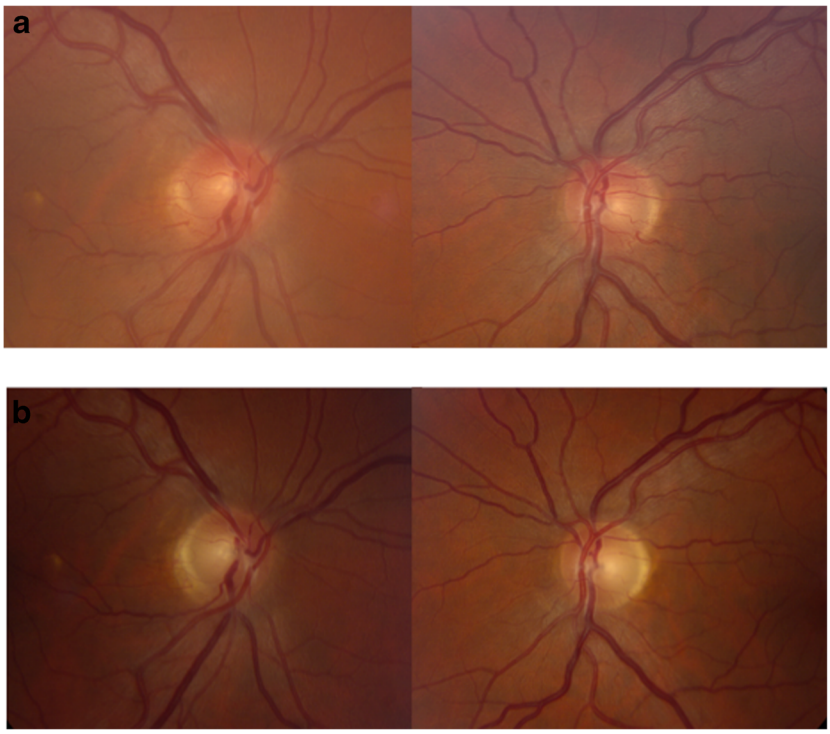

Fig. 1. Optic disc photographs of a 49-year-old male with nutritional optic neuropathy. **a** Before treatment with thiamine and vitamin B_{12} the vision was 6/24 right and 6/60 left; the discs are hyperaemic with subtle blurring of the disc margins. **b** Five weeks following the commencement of treatment the vision was 6/9 right and 6/12 left with resolution of the optic disc hyperaemia and normal disc margins but with developing temporal pallor.

Identify and replace deficient nutrients

It is important to take a detailed history of the types and quantities of foodstuffs that a patient presenting with a potential nutritional optic neuropathy is consuming. The most commonly implicated micronutrient deficiencies in nutritional optic neuropathy are vitamin B_{12}, thiamine (vitamin B_1) and copper. However, it may not be as simple as identifying a single plasma micronutrient deficiency. During the Cuban epidemic, there was not a single micronutrient that was responsible for the development of optic neuropathy amongst so many in the population. Due to the longstanding trade embargo and the later collapse of trade links with Eastern Europe, there was a sudden and abrupt decrease in the quality and quantity of available foodstuffs [6, 19]. Factors found to be important were a lack of variety in the diet, a lack of animal protein, high levels of sugar (constituting > 15% total calorie intake) and staples of rice and beans with limited access to vegetables [7, 20, 21]. Micronutrients which did seem to be important in the Cuban epidemic included thiamine (vitamin B_1), riboflavin (vitamin B_2), niacin (vitamin B_3), vitamin B_{12} (cobalamins), folate (vitamin B_9), methionine, and anti-oxidant carotenoids [4, 10, 22, 23]. Following the national distribution of multi-vitamins in Cuba, the incidence of nutritional optic neuropathy fell dramatically, although some have argued that this was in fact due to the relaxation of trading laws and opening of markets

bringing the ready availability of a wider variety of foodstuffs once again [24]. It seems clear from the Cuban experience that a lack of availability and variety of food puts individuals and populations at risk.

Following bariatric surgery, individuals may be deficient in vitamins B_1, B_6, B_{12}, iron, vitamin D, folate, zinc, magnesium and copper [8•, 25•, 26]. The time of presentation of optic neuropathy following bariatric surgery varies according to the responsible vitamin deficiency, with symptoms due to thiamine deficiency occurring at weeks to months post-operatively, several months to a year when due to vitamin B_{12} deficiency, and typically at more than 3 years post-operatively when due to copper deficiency [8•]. People with a vegan diet may be deficient in B complex vitamins (particularly B_{12}, thiamine and folate) as well as vitamins A, D, E, zinc and selenium. Table 1 shows which patient groups are at potential risk of nutritional optic neuropathy and the micronutrients which are likely to be responsible in each case.

We suggest that in patients with suspected nutritional optic neuropathy, all have a full blood count and iron levels, as well as serum levels of vitamins B_1, B_2, B_6, B_{12}, folate and copper checking. Other nutritional factors can then be considered according to the history: for example zinc and magnesium in the case of bariatric surgery; or vitamins A, D, E, zinc and selenium in the case of a vegan diet. Problems with certain assays used to measure serum B_{12} levels have been reported [41, 42]. Furthermore, serum folate and B_{12} levels do not necessarily reflect the tissue levels of folate and B_{12}, such that there can be normal serum levels and diminished tissue levels (termed functional B_{12} or folate deficiency) [43]. In the case of functional folate deficiency, serum homocysteine

Table 1. Micronutrients responsible for optic neuropathy in different patient groups

Patient group at risk of developing nutritional optic neuropathy	Micronutrient likely to be responsible for optic neuropathy	Refs
Alcoholism	B complex vitamins, particularly thiamine and vitamin B_{12}	[27–29]
Veganism or a restricted vegetarian diet without vitamin supplementation	B complex vitamins, particularly thiamine, vitamin B_{12} and folate	[30, 31]
Bariatric surgery, particularly (but not exclusively) bypass surgery	Thiamine, vitamin B_{12} and copper	[8•, 25•, 32, 33]
Diarrhoeal illness (more commonly chronic but may be acute)	Thiamine	[34, 35]
Inflammatory bowel disease or previous gastric or small bowel surgery	Thiamine, folate, B_{12}	[36, 37]
Pernicious anaemia (either at presentation or inadequately treated)	Vitamin B_{12}	[38]
Parenteral nutrition without adequate vitamin supplementation	Thiamine	[19, 36]
Autism with food selectivity; particularly with highly stereotyped diets devoid of animal products	Vitamin B_{12}	[39]
Depression leading to inadequate diet	Folate, vitamin B_{12}	[40]

may be raised and in functional B_{12} deficiency serum or urine methylmalonic acid may be raised [41–43]. A delay in vitamin B_{12} administration because of normal serum levels can lead to permanent neurological damage [44]. Therefore, if there is a suspicion of nutritional optic neuropathy, even if serum levels of B_{12} are normal, and even if other micronutrient deficiencies are detected, we suggest treating empirically with vitamin B_{12}. Suggested treatment regimes according to the suspected micronutrient deficiency are given in Table 2.

Identify and eliminate contributory toxins

Again, lessons have been learnt from the Cuban epidemic where despite the trade difficulties, there was still ready access to tobacco and alcohol. Otherwise, safe levels of toxins became toxic in the face of nutritional deficiencies. Interestingly, the balance of nutrient deficiency and toxins seemed to be important in determining whether patients in the Cuban epidemic developed optic neuropathy, peripheral neuropathy, or mixed optic/peripheral, with the peripheral neuropathy apparently less affected by toxins and more by the nutritional defect when compared with the optic neuropathy [6]. It has been established that cyanide in tobacco and cassava can cause toxic effects on the optic nerve, and because vitamin B_{12} is important in detoxification of cyanide, vitamin B_{12} deficiency will decrease the threshold of damage due to cyanide toxicity [50]. Furthermore, whilst alcohol is not recognised as a toxin causing

Table 2. Suggested treatment regimens for nutritional optic neuropathy according to the suspected micronutrient deficiency

Suspected micronutrient deficiency	Suggested treatment regime	Notes
B_{12}	1 mg hydroxycobalamin intramuscularly daily for 2 weeks, then 1 mg twice weekly until no further improvement and then 1 mg every 1–3 months [29, 45, 46]	Must also give oral folate supplementation (5 mg daily), an oral multivitamin is also recommended long-term [10, 46]
Thiamine	100 mg thiamine intravenously or intramuscularly daily for 2 weeks, then oral vitamin B complex supplementation daily [27, 35]	If occurring with Wernicke-Korsakoff encephalopathy much higher doses of thiamine may be indicated (e.g., 500 mg daily) and this can be given intravenously with ascorbic acid [45]
Copper	2 mg oral daily (can be given intravenously in the acute phase) [25•, 47]	Zinc and iron can interfere with copper absorption, so consider stopping these, particularly if excess ingestion is suspected [48, 49] Also consider im hydroxycobalamin and oral vitamin B complex supplements
Unknown/no specific deficiency found	1 mg hydroxycobalamin intramuscularly for 2 weeks with oral vitamin B complex supplementation including folate [50]	Ongoing treatment can be tailored according to any improvement or lack thereof seen

optic neuropathy per se (patients who have their vitamin deficiencies corrected but continue to drink have their optic neuropathy rectified) [51, 52], it causes gut irritation and poor liver function, which in turn can limit absorption and cause nutrient deficiencies. It is therefore important to ask about alcohol intake in the case of suspected nutritional optic neuropathy [53•]. Other toxins known to contribute to optic neuropathy are lead, methanol, and some drugs (including ethambutol, amiodarone, and isoniazid). Therefore, it is important to consider toxic neuropathy due to new medicines, as withdrawal of an offending medication can lead to visual recovery [11, 54, 55].

Any identified toxins should be eliminated, and help with smoking cessation should be offered to patients who smoke. One should be wary of the patient who is a mild–moderate smoker and drinker with an apparently normal diet, or only minor dietary deficiencies, as they can still be seriously deficient in vitamin B_{12} or folate [40, 46].

Identify contributory genetic factors and counsel accordingly

It has been argued that many historical cases of tobacco-alcohol amblyopia could in fact have been cases of Leber hereditary optic neuropathy where smoking (and potentially alcohol) played a part in precipitation of the disease [13, 14]. Genetic mitochondrial optic neuropathies can certainly be exacerbated or triggered by toxic or nutritional factors [56]. The clinical characteristics of Leber hereditary optic neuropathies and nutritional or toxic optic neuropathies are essentially indistinguishable. Therefore, testing for the three most common mitochondrial DNA point mutations causing Leber's is advisable in any patient without rapid visual recovery following appropriate nutritional replacement and toxin elimination [12, 56, 57]. The prognosis of Leber hereditary optic neuropathy is generally poorer than that of a nutritional optic neuropathy, and so appropriate counselling and support need to be offered if there is a confirmed hereditary optic neuropathy. Genetic counselling for the index case and family members should also be offered. There are various novel therapies on the horizon for Leber hereditary optic neuropathy, including quinones, gene therapy, antioxidants, near-infrared therapy and stem-cell therapy [12].

A holistic approach to treatment

The management of individuals with nutritional optic neuropathies will often require more than correction of serological abnormalities. Factors such as low mood, negative social circumstances and lack of social support may well play a role [40]. It is important to address these with the help of other health and social care providers in order to 'treat' patients with nutritional optic neuropathy.

When considering populations who are at risk from nutritional optic neuropathy, the public health implications are far-reaching. Physicians recognised that solving the problem of the Cuban epidemic nutritional optic neuropathy was far more complex than simply nutritional supplementation—international social, political and economic problems were implicated in its cause, and these problems needed to be addressed in finding the solution [23, 24, 58–60].

Outcomes

Outcomes from nutritional optic neuropathy will depend on the time course and severity of the nutritional deficit. At best, there can be almost complete recovery of vision [25•, 32, 34, 35], and at worst no recovery at all [31, 47]. Visual acuity will generally return first, followed by colour vision (the reverse of what happens at the onset of disease) [54]. Recovery is generally seen fairly promptly once nutritional supplementation is started (1–4 weeks), although it may take several months to a year for maximal visual recovery [25•, 32, 34, 35]. Outcomes for the 50,000 patients affected by Cuban epidemic optic neuropathy were excellent, with less than 10% having ongoing visual sequelae, less than 1% having a final best-corrected decimal visual acuity less than 0.3 (Snellen equivalent 6/18) and less than 0.1% patients having a final best corrected visual acuity worse than 0.1 (Snellen equivalent 6/60) [6]. Indeed, there were many cases of excellent visual recovery despite significant optic atrophy [10]. However, significant optic atrophy at the time of presentation is likely to be a predictor of poor visual recovery and should lead to a guarded prognosis [31].

There may be reasons why limited recovery is seen for some patients; for example, there may be an unrecognised hereditary mitochondrial optic neuropathy [57]. Given the difficulties interpreting vitamin B_{12} serology, we hypothesise that undertreating vitamin B_{12} deficiency could be another reason for limited recovery in some patients.

Sharma and Sharma recommend a follow-up schedule for patients with nutritional optic neuropathy of 4–6 weeks initially and then, depending on recovery, every 6–12 months [54]. We suggest that initial follow-up may be slightly closer than this, whilst the practitioner confirms that the nutrient replacement is correcting any visual deficit. So, we would recommend an initial follow-up period of 1–2 weeks, extending to 4–6 weeks if there is improvement and then further extending to 6–12 months.

Conclusions

Nutritional optic neuropathy is a relatively rare condition in the developed world, our current understanding of which has been significantly aided by well-investigated epidemics through history, most notably the Cuban epidemic. It has a similar clinical presentation and pathophysiology to other mitochondrial optic neuropathies including toxic and inherited optic neuropathies. The mainstay of treatment for nutritional optic neuropathy is to identify and replace deficient nutrients, the most commonly implicated being vitamins B_{12}, B_1 and copper. One needs to be cautious with the interpretation of serum B_{12} levels as they do not necessarily reflect tissue B_{12} levels. It is therefore wise to treat for a B_{12} deficiency even in the absence of an abnormal serum level when a nutritional optic nerve deficiency is suspected. Toxins including drugs and tobacco have an important part to play in nutritional optic neuropathy, as does alcohol consumption by its effect on diet and gut absorption. Outcomes from nutritional optic neuropathy are variable,

but if treated adequately and early, and there is no genetic cause for the optic neuropathy, the visual prognosis can be very good.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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