

SCIENTIFIC COMMENTARIES

Treatment of Leber hereditary optic neuropathy

A 20-year-old otherwise healthy male, with a known family history of Leber hereditary optic neuropathy (LHON) presents with acute visual loss in one eye. He is accompanied at his appointment by his elder brother who lost vision in both eyes 3 years earlier and by his sister who is asymptomatic. They all ask you what can possibly be done.

The past two decades have witnessed remarkable advances in our understanding of the clinical presentation, genetics and even the pathophysiology of LHON, a maternally inherited cause of usually blinding bilateral visual loss caused by point mutations in the mitochondrial DNA (Newman, 2005; Yu-Wai-Man *et al.*, 2009, 2011; Fraser *et al.*, 2010). However, investigations into potential therapies for LHON and other mitochondrial disorders are still in their nascency. In this issue of *Brain*, Klopstock *et al.* (2011) report on the first randomized placebo-controlled treatment trial of any agent in patients with LHON. This trial also represents one of the first adequately powered randomized controlled treatment trials for any mitochondrial DNA disease.

In most patients with LHON, visual loss is devastating and permanent, with acuities typically worse than 20/200 in both eyes (Newman, 2005; Yu-Wai-Man *et al.*, 2009, 2011; Fraser *et al.*, 2010). Approximately 50% of patients with visual loss from LHON will experience sequential eye symptoms, with intervals between affected eyes ranging from days to months, but typically at an interval of 2–4 months (Newman *et al.*, 1991; Riordan-Eva *et al.*, 1995). At least 97% of patients with visual loss in one eye will have the second eye involved within 1 year (Newman *et al.*, 2005). In some patients, visual recovery may occur after acute visual loss, sometimes manifested as a 'fenestration' within a visual field defect (the so-called donut or bagel scotoma) or with more diffuse return of central visual acuity and colour vision, usually bilaterally (Stone *et al.*, 1992; Riordan-Eva *et al.*, 1995; Newman, 2005). Visual recovery, when it occurs, generally happens slowly between 6 and 12 months after the onset of visual loss; however, sudden dramatic improvement in vision may occur many years after symptom onset (Stone *et al.*, 1992; Newman, 2005).

The most important prognostic factor for visual recovery in patients with LHON is a favourable mutation status. Indeed, among the three primary LHON mutations, clinical phenotype is virtually indistinguishable, with the only consistent mutation-dependent clinical feature being the prognosis for spontaneous recovery of visual acuity. The '14484' mutation has a 37–71%

chance of some degree of visual improvement, whereas the '11778' mutation has only a 4% chance (Stone *et al.*, 1992; Oostra *et al.*, 1994; Riordan-Eva *et al.*, 1995; Newman, 2005). The '3460' mutation appears to have the same chance of recovery as the '11778' mutation, but numbers are too small for meaningful comparison. An additional positive prognostic feature is an age of onset <20 years, and especially <10 years (Newman, 2005; Barboni *et al.*, 2006). It has also been suggested that thicker retinal nerve fibre layer and larger optic disc vertical diameter on optical coherence tomography may be associated with a better visual prognosis (Barboni *et al.*, 2005, 2006; Ramos *et al.*, 2009). The pathogenesis of LHON likely involves a combination of decreased complex-I driven ATP production, increased free radical production and ultimately retinal ganglion cell apoptosis (Fraser *et al.*, 2010; Yu-Wai-Man *et al.*, 2011).

Proposed treatments for LHON include low vision aids, avoidance of potential precipitants of visual loss, general therapies for mitochondrial disorders, anti-apoptotic agents and a variety of gene therapies (Fraser *et al.*, 2010; Yu-Wai-Man *et al.*, 2011). Symptomatic treatments should be considered in all patients with vision-impairing optic neuropathies to improve quality of life, in particular to aid with reading, communication, gainful employment, navigation and self-operation of a motor vehicle. Low vision aids may benefit patients with severe vision loss from optic neuropathies. In particular, patients with LHON are often young adults with preserved peripheral vision, who make excellent candidates for low vision rehabilitation.

Although avoiding agents that may act as mitochondrial 'stressors' is a non-specific recommendation for all patients with disorders having a presumed mitochondrial pathophysiology, there is no study that has shown proven benefit (Chinnery *et al.*, 2006). One recent epidemiological study suggested that vision loss does indeed occur more often in individuals at risk for LHON who smoke, and possibly those with heavy alcohol intake (Kirkman *et al.*, 2009). It is, therefore, prudent to caution patients to avoid tobacco use, excessive alcohol intake, cyanide-containing products, medications that may have mitochondrial toxicity and environmental toxins, especially during the acute phase of visual loss (Newman, 2009).

Directed therapies for mitochondrial disorders are very limited. A 2006 Cochrane review of 678 abstracts and articles found no evidence supporting any intervention in the management of mitochondrial disease (Chinnery *et al.*, 2006). General therapies

that have been suggested for the treatment of mitochondrial disease include: vitamins and cofactors [coenzyme Q₁₀ (CoQ₁₀), folic acid, vitamin B12, thiamine, riboflavin, L-carnitine, L-arginine and creatine]; electron acceptors (vitamin C, menadiol); free radical scavengers (CoQ₁₀, idebenone, alpha-lipoic acid, minocycline, cyclosporine A, glutathione and vitamin E); and inhibitors of toxic metabolites (dichloroacetate) (DiMauro and Mancuso, 2007; Fraser *et al.*, 2010). Most of these general therapies are harmless at their usual doses, although some may be expensive. In the absence of any other proven therapy in mitochondrial disease, many clinicians resort, on theoretical or anecdotal grounds alone, to 'mitochondrial cocktails'—various combinations of these agents—to treat their patients. For example, the combination of creatine (3 g b.i.d., i.e. twice a day), CoQ₁₀ (120 mg b.i.d.) and alpha-lipoic acid (300 mg b.i.d.) was shown to reduce serum lactate and markers of oxidative stress in patients with mitochondrial cytopathies in one randomized double-blind controlled trial, probably through a free radical-scavenging mechanism (Rodríguez *et al.*, 2007).

Gene therapy shows significant promise in the treatment of mitochondrial diseases (DiMauro *et al.*, 2007; Fraser *et al.*, 2010; Koilkonda and Guy, 2011; Yu-Wai-Man *et al.*, 2011). Many ingenious strategies have been devised, including 'gene shifting' for heteroplasmic disorders; 'allotopic rescue' in which the nuclear genome is transfected by a genetically engineered vector to express a protein usually encoded by the mitochondrial genome, which is then transported into the mitochondria to replace or complement a protein expressed by mutated mitochondrial DNA (Koilkonda and Guy, 2011); complementation of nuclear genes that code for proteins that enhance endogenous mitochondrial antioxidant mechanisms (Koilkonda and Guy, 2011); and nuclear transfer techniques in which the entire mitochondrial genome of an oocyte from a female with a known mitochondrial DNA mutation is replaced *in vitro*, followed by fertilization and implantation for normal embryo development (Tachibana *et al.*, 2009; Craven *et al.*, 2010).

LHON offers a unique 'laboratory' for the investigation of new interventions in mitochondrial disease. Since LHON vision loss often occurs in a bilateral sequential fashion, a window of opportunity exists for possible therapeutic intervention after vision loss in the first eye but before second eye involvement (Newman *et al.*, 2005). LHON has the additional desired property that drugs, gene vectors and other agents may be easily and directly delivered to the tissue at risk, the retinal ganglion cells and optic nerve, by vitreous injection. Although LHON alone presents this opportunity for experimentation, intervention studies in this 'laboratory' have enormous potential for generalization to other mitochondrial diseases, and perhaps to apoptosis-mediated diseases as a whole, including the acquired optic neuropathies (Fraser *et al.*, 2010).

In light of the possibility for spontaneous recovery in some patients with LHON, any anecdotal reports of treatment efficacy must be considered with caution. The older literature includes attempts to treat or prevent the acute phase of visual loss with systemic steroids, hydroxycobalamin and cyanide antagonists, none of which have proved effective (Newman, 2005). In the 1960s, reports from Japan advocated craniotomy with the lysis

of chiasmal arachnoid adhesions in patients with LHON, with 80% of more than 120 patients reporting visual improvement (Imachi, 1967; Imachi and Nishizaki, 1970). Although the data are impressive, no further reports have followed, and it is difficult to support a surgical therapy logistically removed from the site of ocular neurovascular changes and of presumed primary involvement (the retinal ganglion cells). Brimonidine purite, an α -2 agonist with purported anti-apoptotic effects on retinal ganglion cells, proved non-efficacious as a prophylactic agent for second eye visual loss in LHON in an open-labelled, non-randomized, multi-centre study of nine patients (Newman *et al.*, 2005).

Idebenone, a short-chain benzoquinone structurally related to CoQ₁₀, readily enters the brain and localizes to the mitochondria. It both stimulates net ATP formation and acts as a potent free radical scavenger protecting the mitochondrial membrane against lipid peroxidation. Compared with other analogues of coenzyme Q, idebenone is particularly suited for bypassing the functional impairment of mitochondrial complex I (the three primary mitochondrial DNA LHON mutations are located in protein coding genes of complex I). Initial reports of idebenone use in Friedreich ataxia suggested a beneficial effect on both cardiac and neurological symptoms, especially at high doses (Mariotti *et al.*, 2003; Di Prospero *et al.*, 2007). However, subsequent trials have been disappointing (Lynch *et al.*, 2010; Lagedrost *et al.*, 2011). Neutropenia may be a rare side-effect of idebenone.

Mashima *et al.* (1992) reported the case of a 10-year-old male homoplasmic for the '11778' mutation who had early improvement in both eyes after 1 year of oral therapy with idebenone, but such an early age of onset certainly could have predisposed this child to spontaneous recovery. Other single case reports also raised the possibility of a beneficial effect of idebenone on visual and neurological recovery (Cortelli *et al.*, 1997; Carelli *et al.*, 1998). Mashima *et al.* (2000) reported on 28 patients with LHON, 14 of whom were treated with idebenone combined with vitamin B2 and vitamin C. There was no significant difference in the number of eyes with visual recovery, although the authors claimed that the treatment seemed to speed recovery when it occurred. Barnils *et al.* (2007) found no beneficial effects of large doses of idebenone and vitamin C and riboflavin in the prevention of second eye involvement in two patients with LHON harbouring the '11778' mutation.

In an online Letter to the Editor in this issue of *Brain*, Carelli *et al.* (2011) retrospectively review the largest cohort of idebenone-treated patients with LHON to date (44 patients) and compare them to 59 untreated patients with LHON. All patients were older than 10 years, within 1 year of the onset of visual loss and had a follow-up of at least 5 years. The patients were not randomized to treatment or no treatment, but all untreated patients were initially seen prior to idebenone availability, and all treated patients were systematically treated with idebenone after a certain point in time when the drug became available, mitigating against some of the lack of standardization inevitable in retrospective studies. The dosing of the drug was variable and not controlled, ranging from 270 to 675 mg/day. The authors reported an increased frequency of visual recovery in the treated compared with the untreated patients with the '11778' mutation, and recovery of vision was significantly associated with early administration

of therapy. Although the six patients treated with idebenone prior to second eye involvement had an apparent delay in visual loss in the second eye, none of these second eyes remained uninvolved or significantly better as regards their ultimate visual function.

Klopstock *et al.* (2011) report the results of a 24-week international multi-centre, double-blind, randomized placebo-controlled trial of 85 patients with LHON due to one of the three common primary mitochondrial DNA mutations associated with the disease, in which 55 patients were treated with idebenone (900 mg/day) and 30 with placebo. Unfortunately, the original plan to enrol patients in the acute phase of LHON soon after first eye involvement proved challenging due to poor recruitment. Instead, patients with LHON older than 13 and younger than 65 years, with visual loss for up to 5 years were enrolled. None of the primary (best recovery in visual acuity) nor secondary end points (change in best visual acuity, change in visual acuity of the best eye at baseline and change in visual acuity for both eyes in each patient) reached statistical significance in the intention-to-treat population, although there was a trend towards better visual outcomes, especially if patients with the '14484' mutation (associated with a high rate of spontaneous recovery and better visual outcomes) were excluded. On a practical level, this trend translates to approximately one Snellen line difference between treated and untreated patients. However, *post hoc* interaction subgroup analysis of patients with a discordant visual acuity at baseline showed statistically significant secondary end points between the idebenone and placebo groups, translating to about a 4 or 5 Snellen line difference in vision. The drug was deemed safe and well tolerated.

There are several weaknesses of the trial, including the relatively small numbers of patients (thereby limiting the power of the analyses); the inclusion of patients with visual loss as long as 5 years prior to the initiation of treatment, with 65% reporting symptoms for >1 year (hence reducing the likelihood of meaningful recovery in patients in whom optic atrophy had ensued); and the inclusion of patients with the '14484' mutation (with their higher chance for spontaneous recovery). The lack of follow-up beyond 24 weeks may also have mitigated against more positive results, especially given Carelli *et al.*'s (2011) suggestion that the longer the duration of idebenone treatment and the earlier it is begun, the better the visual outcome. However, although idebenone appeared to delay the onset of second eye involvement in those patients in the Carelli *et al.* (2011) study with discordant visual acuities at the time of initial treatment, all the treated patients ultimately had second eye involvement, presumably eventually equivalent to the first (Carelli *et al.*, 2011), suggesting that longer follow-up in the Klopstock *et al.* (2011) study might actually have resulted in less impressive results among this subgroup of patients.

All limitations notwithstanding, and despite the lack of dramatically positive results in either the retrospective or the randomized prospective studies of idebenone treatment of patients with LHON, any suggestion of efficacy in the treatment of this nearly uniformly blinding disorder must be viewed as encouraging. As our understanding of the underlying pathophysiology of LHON and other mitochondrial DNA diseases improves, other more directed therapies should emerge and be tested in a prospective,

randomized and controlled manner akin to the Klopstock *et al.* (2011) study. Until then, it is reasonable to consider idebenone therapy in patients with LHON such as the young male described in the opening paragraph who presents early in the onset of his disease. Treatment of his long-affected brother would be less compelling and unlikely to result in clinically meaningful improvement. Treatment of his asymptomatic sister currently seems ill advised.

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Sense and sensitivity of novel criteria for frontotemporal dementia

The story goes that when Marco Polo first saw a rhinoceros on Java, he called it a unicorn. As a meticulous observer, he hastened to tell us that these unicorns appeared rather strange (Eco, 2000). Diagnostic categories in medicine guide our attention to discriminating nosological features and prevent us from misidentifying rare disease entities as more familiar diseases they may resemble. Interest in frontotemporal dementia (FTD) was rekindled in the late 1980s when patterns of hypoperfusion and hypometabolism distinct from those seen in functional images of Alzheimer's disease were noted (Neary *et al.*, 1987, 1988). Clinicopathological series collected in Lund and Manchester and international conferences on FTD in Lund led to the Lund–Manchester criteria for frontotemporal lobar degeneration (FTLD: Brun *et al.*, 1994; Neary *et al.*, 1998) suggesting a common denominator for three different phenotypical presentations: FTD, in which behavioural

and personality changes predominate; progressive non-fluent aphasia; and semantic dementia. Other authors have since proposed restricting the term FTLD to neuropathologically confirmed disease (Josephs *et al.*, 2011). The clinical neurological examination in FTD can remain essentially normal until well into the disease course. The history provided, however, often abounds with concrete examples of changes in personal and social conduct that together may be expressed as a qualitative difference in the patient's personality. The Lund–Manchester papers (Neary *et al.*, 1987, 1988, 1998; Brun *et al.*, 1994) provided clinicians with a vocabulary that allowed these complex patterns to be encapsulated in discrete components: five core features, and an 11-item list of supportive features and nine exclusionary clinical features. According to the literal interpretation, each of the five core criteria and none of the exclusionary features must be present. While this