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Weighing in on Leber hereditary optic neuropathy: effects of mitochondrial mass

Among mitochondrial diseases, Leber hereditary optic neuropathy (LHON) stands out as a prototype in several respects. It was the first mitochondrial disease to be clinically recognized by Dr Albrecht von Graefe (1858) but was named after Dr Theodore Leber who, 13 years after the original report, described 15 patients with the disease, from four different families (Leber, 1871). LHON also has the distinction of being the initial human disorder noted to be maternally inherited (Wallace, 1970) and the first to be linked to a pathogenic point mutation of mitochondrial DNA (Wallace *et al*., 1988).

This common mitochondrial disease typically presents in males during adolescence or young adulthood with painless loss of central vision in one eye, followed by loss of vision in the second eye within weeks or months (Newman, 2005; Barboni *et al*., 2010). The loss of vision is because of selective vulnerability of retinal ganglion cells in the papillomacular bundle. In the majority of cases, LHON is a result of one of three mitochondrial DNA point mutations within genes encoding polypeptide subunits of complex I of the mitochondrial respiratory chain. Unlike most mitochondrial DNA mutations, which are heteroplasmic (a mixture of both mutant and normal mitochondrial genomes) in the majority of patients, LHON mutations are homoplasmic (only mutant mitochondrial DNA is present). Despite the early recognition of this mitochondrial disease and its cause, many features of LHON are still unknown.

One of the most vexing features of LHON mutations is their incomplete inheritance; thus, all matrilineal members of a LHON pedigree carry the pathogenic mitochondrial DNA genotype, but only some individuals develop the blindness. Previously, the team led by Drs Valerio Carelli and Carla Giordano reported that oestrogens improved mitochondrial dysfunction in cultured cells harbouring LHON mutations, thereby providing an explanation for the predominance of males affected by this disease (Giordano *et al*., 2011).

In this issue of *Brain*, Giordano *et al*. (2014) report elegant results indicating that increased mass of mitochondria is neuroprotective in unaffected carriers of LHON mutations. Mitochondrial proliferation is a well recognized phenomenon in many mitochondrial diseases and manifests as ragged-red fibres in muscle biopsies (DiMauro and Schon, 2008). The ragged-red fibres are striking in skeletal muscle treated with the modified Gomori trichrome stain that highlights the abundant mitochondria in the subsarcolemmal regions of muscle fibres. This histological hallmark of mitochondrial diseases is most often observed in patients with mitochondrial DNA point mutations or large-scale deletions that affect transfer RNA genes required for mitochondrial protein synthesis. In contrast, when mitochondrial DNA point mutations affect genes encoding polypeptide subunits of the mitochondrial respiratory chain, ragged-red fibres are often not seen, as is the case in LHON. Nevertheless, subtle subsarcolemmal increases in mitochondria were observed in muscle and blood cells of patients with LHON (Larsson *et al*., 1991) but largely ignored by investigators in the field.

Giordano *et al*. (2014) not only noted the earlier reports of increased mitochondrial mass in cells of patients with LHON, they also performed meticulous analyses of mitochondria mass in cells and tissues of a large cohort of affected and carrier individuals with LHON mutations. Surprisingly, they observed that the average mitochondrial DNA content in white blood cells of LHON patients was twice as high as the mean mitochondrial DNA content in healthy controls whereas asymptomatic LHON mutation carriers had about three times more mitochondrial DNA in leucocytes compared with controls. They recorded similar increases in mitochondrial DNA in muscle and cultured fibroblasts of LHON mutation carriers and patients, as well as increases in mitochondrial transcripts, respiratory chain proteins and enzyme activities, and biogenesis factors relative to controls indicating a generalized increase in mitochondria rather than just mitochondrial DNA. The high mitochondrial DNA content in leucocytes was associated with milder subclinical signs of ocular pathology (e.g. temporal retinal nerve fibre thickness assessed by ocular coherence tomography) while pathological studies of a single asymptomatic LHON mutation carrier revealed increased mitochondrial DNA level in the vulnerable macular retinal ganglion cells further suggesting that increased mitochondrial mass is protective against the adverse effects of LHON mutations. Functional studies of fibroblasts demonstrated that after stress, cells from asymptomatic mutation carriers activated mitochondrial biogenesis and mitochondrial DNA

replication more effectively than cells from patients with LHON. Collectively, these findings indicate that mitochondrial mass increases in response to LHON mutations and large increases may be protective in asymptomatic carriers. Presumably, the increased amount of mitochondrial compensates for the defect of respiratory chain complex I in the patients.

Although this excellent translational research study by Giordano *et al*. (2014) strongly supports the notion that mitochondrial biogenesis is protective in LHON, proof of this concept will require identification of the factor(s) responsible for activating mitochondrial proliferation and experimental manipulation of the biogenesis factors in cells and animal models. If validated and extended, these observations will have clinical diagnostic and therapeutic implications, as noted by the authors. For example, they note that levels of mitochondrial DNA in white blood cells of LHON mutation carriers may prove to be a biomarker predictive of developing blindness. Identification of the pathway responsible for mitochondrial DNA biogenesis will provide a pharmacological target to prevent blindness in unaffected mutation carriers. Studies have already demonstrated promising therapeutic effects of activating mitochondrial biogenesis in mouse models of mitochondrial diseases with defects of the respiratory chain (Wenz *et al*., 2008; Viscomi *et al*., 2011). Remarkably, Giordano *et al*. have shown that asymptomatic LHON mutation carriers may already be taking advantage of enhancing mitochondrial mass to prevent blindness.

Michio Hirano, MD
Columbia University Medical Centre
New York, NY USA
E-mail: mh29@cumc.columbia.edu

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Syncope: how the EEG helps in understanding clinical findings

Although it is now widely accepted that the key to accurate diagnosis and risk stratification of syncope is a thoughtful and scrupulous history, exactly what is meant by the history remains unclear, and moving it from experts to front-line workers has proven difficult. Partly this is because syncope is simply a symptom, like fever, with a plethora of potential causes. Partly as well this reflects the multitude of somewhat overlapping symptoms and signs for the most common form, the 'faint' or vasovagal syncope. There are several clinical features that are known to be helpful in the differential diagnosis of loss of consciousnesses, based on quantitative symptom studies. These for example help distinguish epileptic convulsions and pseudosyncope from syncope, but such studies were aimed at clinical decision-making. They reported just the most highly significant clinical points and do not help clinicians make sense of the welter of symptoms that clinical experience suggests (Sheldon *et al.*, 2002, 2006; Wieling *et al.*, 2009; Tannemaat *et al.*, 2013).

In this issue of *Brain*, van Dijk *et al.* (2014) provide fascinating and informative insights into why some symptoms cluster with each other in patients with vasovagal syncope. The authors performed detailed EEG and videometric analyses of 69 patients with positive responses to head-up tilt table testing. The EEG provides an objective marker of brain dysfunction during the cerebral hypoperfusion that accompanies syncope. For nearly 60 years investigators have described EEG patterns during provoked reflex syncope (Gastaut and Fischer-Williams, 1957; Ammirati *et al.*, 1998; Sheldon *et al.*, 1998; Martinez-Fernandez *et al.*, 2008). Two patterns have been described. A 'slow-flat-slow' pattern is characterized by an initial slow phase in which delta waves appear and wave amplitude increases, a sudden flattening of the EEG, and a return to normal brain activity through a slow phase.