doi:10.1093/brain/awp195 Brain 2009: 132; 2306–2308 | 2306

BRAIN
A JOURNAL OF NEUROLOGY

SCIENTIFIC COMMENTARY

Leber hereditary optic neuropathy: bad habits, bad vision?

The puzzle that Leber hereditary optic neuropathy (LHON) represents has not been completely solved for over 250 years, despite 20 recent years of rapid advances in mitochondrial genetics (Newman, 2005; Yu-Wai-Man *et al*., 2009). Although the majority of the underlying causative point mutations in mitochondrial DNA (mtDNA) have been identified, we still cannot answer the most fundamental questions about this disease (Newman, 2002). Why does not everyone who carries a LHON mitochondrial DNA point mutation have visual loss in their lifetime? Why are males affected more often than females? Why does visual loss occur so preferentially during the second and third decades of life, and so infrequently past the age of 50? What accounts for such an abrupt and catastrophic loss of vision, either simultaneously or sequentially, within weeks to months? And, finally, what is so special about the optic nerve, and presumably the retinal ganglion cells, that makes these structures so exclusively sensitive to an abnormality in mitochondrial DNA, when this is present in every cell of the body?

Researchers have proposed multiple theories to account for these unusual features of LHON, only very few of which have been proven. Regarding possible genetic/epigenetic factors, the presence of a primary mitochondrial DNA mutation, primarily those at nucleotide positions 11 778, 14 484 or 3460, is necessary but not sufficient for the phenotypic expression of the disorder (Yu-Wai-Man *et al*., 2009). Heteroplasmy, presumably in the retinal ganglion cells, may diminish the chances of visual loss, but even homoplasmy cannot of itself account for most cases of LHON (Chinnery *et al*., 2001). Certain mtDNA background haplotypes may influence expression (Hudson *et al*., 2007), in particular haplotype J for the 11 778 and 14 484 mutations and haplotype K for the 3460 mutation; yet still, the majority of the carriers will not experience visual loss in their lifetime. Additionally, nuclear genetic influences have been proposed, the most logical of which would localize a pathological mutation to the X chromosome, explaining the striking male predominance in LHON expression (Hudson *et al*., 2005; Shankar *et al*., 2008). However, discordance in sets of male monozygotic twins with LHON primary mutations (Johns *et al*., 1993; Biousse *et al*., 1997) further supports a role for non-genetic factors influencing LHON expression.

Factors that have been proposed as precipitating LHON visual loss include both internal and external environmental triggers (Newman, 2005; Yu-Wai-Man *et al*., 2009). Among the former are systemic illnesses such as diabetes mellitus, nutritional deficiencies, psychological stress, metabolic disturbances or variations in normal physiological or hormonal status. Proposed external environmental factors include head trauma, industrial toxins, medications (in particular, the anti-retroviral and anti-mycobacterial drugs) and of course tobacco and alcohol. None of these factors has been proven to be causal, although the literature is most replete with reports on smoking and drinking alcohol but with conflicting results (Cullom *et al*., 1993; Riordan-Eva *et al*., 1995; Chalmers and Harding, 1996; Tsao *et al*., 1999; Kerrison *et al*., 2000; Sadun *et al*., 2003).

In this issue of *Brain*, Kirkman *et al*. (2009) report the results of the largest epidemiological study, to date, investigating the role of smoking and alcohol exposure in the expression of visual loss in LHON. A structured telephone interview was conducted on 196 affected and 206 unaffected carriers from 125 LHON pedigrees defined by one of the three primary mtDNA mutations. Unlike all but one of the previous case–control studies (Kerrison *et al*., 2000), efforts were made to assess exposure levels prior to the onset of visual loss. This is especially important when one considers that patients recently struck blind may have psychological reasons for increased substance abuse, as well as more time on their hands once occupationally disabled. The authors found that smoking is associated with an increased rate of visual loss, and that this relationship might even be dose responsive. The authors also identify a trend towards increased visual failure with alcohol use, but only with heavy intake. Based on these results, the authors conclude that smoking has a consistent role in increasing disease penetrance in LHON and that asymptomatic LHON carriers should be strongly advised not to smoke and also to avoid binge drinking—perhaps wise advice for us all!

As with all studies of this nature, there are limitations to the results reported by Kirkman *et al*. (2009). Primarily, this study did not control for pedigree. Unlike the analysis performed by Kerrison *et al*. (2000), albeit smaller, which included at least one affected and one unaffected person from each pedigree and therefore assessed concordance within families, the current study compared

all the affected patients from 125 pedigrees to all those unaffected, without controlling specifically for their familial relationship. Because family members are likely to share common genetic and environmental influences for tobacco and alcohol consumption, as well as common genetic risk factors for visual loss, the observed associations could reflect a classic confounding effect. It is also worth noting that the survival curve for heavy cumulative smoking actually shows a potentially protective benefit until the age of around 55 years (Kirkman *et al*., 2009; Fig. 3A). Interestingly, somewhat similar but less prominent effects were also described by Kerrison *et al*. (2000). These findings could reflect a survivor bias: because a long-lived individual is more likely to have higher cumulative consumption, this group would be expected to have a greater proportion of patients showing onset of visual loss at a later age. Alternatively, this 'protective' effect of smoking could represent a true biological effect exposure. Many compensatory mechanisms are activated to prevent oxidative damage when people are chronically exposed to toxins, and the activation of these pathways may protect chronic users, at least for a while. This hypothesis could also explain why, if acute exposure to high levels leads to severe damage before these temporarily protective pathways have had time to reach full capacity, high intensity smokers have an earlier age of onset. Finally, it is also possible that, by chance, the group of heavy cumulative smokers included a disproportionate number of individuals from pedigrees with a low intrinsic risk of visual loss, perhaps because of a more protective nuclear or mitochondrial genome, and therefore only resulting in visual failure after many years of smoking.

The possible pathophysiological basis for the effect of smoking on triggering visual loss in LHON is nicely reviewed in the Kirkman *et al*., (2009) article, and probably relates to the deleterious effects of smoking on various aspects of mitochondrial biogenesis, thereby taxing an already susceptible optic nerve. To my knowledge, no studies of the possible influence of smoking on the expression of visual loss in dominant optic atrophy, a nuclear-inherited mitochondrial optic neuropathy, have been performed. Similarly, the potential additional toxicity of smoking in patients with those acquired optic neuropathies in which a final common pathway of mitochondrial dysfunction is suspected, remains speculative (Foulds *et al*., 1969; Rizzo, 1995; Carelli *et al*., 2004).

Can the findings of this study shed any light on the entity once known as 'tobacco-alcohol amblyopia', in which visual loss from bilateral optic neuropathy, almost exclusively in men, was blamed on smoking and drinking (Rizzo and Lessell, 1993; Solberg *et al*., 1998)? The actual existence of an optic neuropathy that results from the combined toxicities of tobacco and alcohol has been challenged for years. Most experts would now agree that alcohol has no proven toxic effects on the optic nerve and that its inclusion in this setting was a result of the confounding coexistence of smoking and drinking (Lessell, 1998). On the other hand, a toxic effect of smoking on the optic nerve probably has some validity, as suggested not only by the current article in *Brain* (Kirkman *et al*., 2009), but also from the results of investigations into the Cuban epidemic optic neuropathy in which tobacco use was an additive risk factor to malnutrition (Cuba Neuropathy Field Investigation Team, 1995). Similarly, 50 years earlier, Schepens (1946) reported an increased prevalence of optic neuropathy among smokers malnourished during the German occupation of Belgium. It is intriguing to propose that all cases of 'tobacco amblyopia' actually reflect the unmasking of an underlying LHON mtDNA mutation (Cullom *et al*., 1993). Systematic screening among those affected with the Cuban optic neuropathy did not find an increased prevalence of any of the LHON primary mtDNA mutations (Newman *et al*., 1994; Torroni *et al*., 1995), and a large LHON pedigree in the province most affected by the epidemic did not see an increased number of individuals with visual loss (Newman *et al*., 1994). Although rare, convincing cases of tobacco optic neuropathy are still encountered without obvious underlying nutritional deficiency, concurrent alternative toxin exposure or known mtDNA abnormality (Cullom *et al*., 1993; Rizzo and Lessell, 1993).

Finally, is there any evidence implicating underlying physiological susceptibility of the male optic nerve to toxic effects from smoking? 'Tobacco amblyopia' is overwhelmingly a disorder of men, but this may be partly explained by its usual occurrence among smokers of cigars and pipes (Lessell, 1998). Epidemic optic neuropathy in Cuba was more common among males, while the peripheral neuropathy component of this disorder was not (Cuba Neuropathy Field Investigation Team, 1995). Additionally, in the Kirkman *et al*. (2009) study, smoking appeared to be a greater risk factor for visual loss in men than for women (Kirkman *et al*., 2009; Fig. 5). Although never systematically studied, it would be interesting to see if other purported toxic optic neuropathies, especially those with a final common pathophysiology of mitochondrial damage (Rizzo, 1995; Carelli *et al*., 2004), occur more frequently among men.

The fact that still remains is that there are many LHON carriers, even males, who smoke and never lose vision in their lifetime. Additionally, there are many children who lose vision from LHON without any conceivable toxic environmental exposure. It is certainly reasonable, however, to counsel carriers of LHON mutations regarding the potential risks of bad habits. The secrets behind expression in LHON remain elusive. This article in *Brain* helps to clear some of the smoke that gets in our eyes.

Acknowledgements

Dr. N.J.N is a recipient of a Research to Prevent Blindness Lew R. Wasserman Merit Award.

Funding

Departmental grant from Research to Prevent Blindness, New York Department of Ophthalmology, partially); Core grants from the National Institute of Health, Bethesda, Maryland (Department of Ophthalmology, Grant no. P30-EY06360).

Nancy J. Newman
Departments of Ophthalmology, Neurology and Neurological Surgery, Emory University School of Medicine, Atlanta, Georgia, USA
E-mail: ophtnjn@emory.edu

References

Biousse V, Brown MD, Newman NJ, Allen JC, Rosenfeld J, Meola G, et al. De novo 14484 mitochondrial DNA mutation in monozygotic twins discordant for Leber's hereditary optic neuropathy. Neurology 1997; 49: 1136–8.

Carelli V, Ross-Cisneros FN, Sadun AA. Mitochondrial dysfunction as a cause of optic neuropathies. Prog Retin Eye Res 2004; 23: 53–89.

Chalmers RM, Harding AE. A case-control study of Leber's hereditary optic neuropathy. Brain 1996; 119: 1481–6.

Chinnery PF, Andrews RM, Turnbull DM, Howell NN. Leber hereditary optic neuropathy: does heteroplasmy influence the inheritance and expression of the G11778A mitochondrial DNA mutation? AM J Med Genet 2001; 98: 235–43.

Cuba Neuropathy Field Investigation Team. Epidemic optic neuropathy in Cuba: clinical characterization and risk factors. N Engl J Med 1995; 333: 1176–82.

Cullom ME, Heher KL, Miller NR, Savino PJ, Johns DR. Leber's hereditary optic neuropathy masquerading as tobacco-alcohol amblyopia. Arch Ophthalmol 1993; 111: 1482–5.

Foulds WS, Chisholm IA, Bronte Stewart JM, et al. Vitamin B12 absorption in tobacco amblyopia. Br J Ophthalmol 1969; 53: 393–7.

Hudson G, Keers S, Yu-Wai-Man P, et al. Identification of an X-chromosomal locus and haplotype modulating the phenotype of a mitochondrial DNA disorder. Am J Hum Genet 2005; 77: 1086–91.

Hudson G, Carelli V, Spruijt L, et al. Clinical expression of Leber hereditry optic neuropathy is affected by the mitochondrial DNA-haplogroup background. Am J Hum Genet 2007; 81: 228–33.

Johns DR, Smith KH, Miller NR, Sulewski ME, Bias WB. Identical twins who are discordant for Leber's hereditary optic neuropathy. Arch Ophthalmol 1993; 111: 1491–4.

Kerrison JB, Miller NR, Hsu F, et al. A case-control study of tobacco and alcohol consumption in Leber hereditary optic neuropathy. Am J Ophthalmol 2000; 130: 803–12.

Kirkman M, Yu-Wai-Man P, Korsten A, et al. Gene-environment interactions in Leber hereditary optic neuropathy. Brain 2009; (in press).

Lessell S. Toxic and deficiency optic neuropathies. In: Miller NR, Newman NJ, editors. Walsh & Hoyt's Clinical Neuro-Ophthalmology. 5th edn., Baltimore: William & Willkins; 1998. p. 663–79.

Newman NJ. Hereditary optic neuropathies. In: Miller NR, Newman NJ, Biousse V, Kerrison JB, editors. Walsh & Hoyt's Clinical Neuro-Ophthalmology. 6th edn., Philadelphia: Lippincott Williams & Williams; 2005. p. 465–501.

Newman NJ. From genotype to phenotype in Leber hereditary optic neuropathy: still more questions than answers. J Neuro-ophthalmol 2002; 22: 257–61.

Newman NJ, Torroni A, Brown MD, et al. Epidemic neuropathy in Cuba not associated with mitochondrial DNA mutations found in Leber's hereditary optic neuropathy patients. Am J Ophthalmol 1994; 118: 158–68.

Riordan-Eva P, Sanders MD, Govan GG, Sweeney MG, Da Costa J, Harding AE. Clinical features of Leber's hereditary optic neuropathy defined by the presence of a pathogenic mitochondrial DNA mutation. Brain 1995; 118: 319–37.

Rizzo JF III. Adenosine triphosphate deficiency: a genre of optic neuropathy. Neurology 1995; 45: 11–16.

Rizzo JF, Lessell S. Tobacco amblyopia. Am J Ophthalmol 1993; 116: 84–7.

Sadun AA, Carelli V, Salomao SR, et al. Extensive investigation of a large Brazilian pedigree of 11778/haplotype J Leber hereditary optic neuropathy. Am J Ophthalmol 2003; 26: 268–72.

Schepens CL. Is tobacco amblyopia a deficiency disease? Trans Ophthalmol Soc UK 1946; 66: 309–31.

Shankar SP, Fingert JH, Carelli V, et al. Evidence for a novel x-linked modifier locus for Leber hereditary optic neuropathy. Ophthalmic Genet 2008; 29: 17–24.

Solberg Y, Rosner M, Belkin M. The association between cigarette smoking and ocular diseases. Surv Ophthalmol 1998; 42: 535–47.

Torroni A, Brown MD, Lott MT, Newman NJ, Wallace DC, the Cuba Neuropathy Field Investigation Team. African, Native American, and European mitochondrial DNAs in Cubans from Pinar del Rio province and implications for the recent epidemic neuropathy in Cuba. Hum Mut 1995; 5: 310–17.

Tsao K, Aitken PA, Johns DR. Smoking as an aetiological factor in a pedigree with Leber's hereditary optic neuropathy. Br J Ophthalmol 1999; 83: 577–81.

Yu-Wai-Man P, Griffiths PG, Hudson G, Chinnery PF. Inherited mitochondrial optic neuropathies. J Med Genet 2009; 46: 145–158.