LETTER

mtDNA mutations in Chilean patients with optic neuropathy

The aetiology of acute unilateral (AUON) and bilateral optic neuropathies (BSON) is unknown in most patients in Chile, after compressive lesions, collagen vascular diseases, and toxin exposure are ruled out. By contrast, up to 85% of white patients with clinically isolated AUON will develop multiple sclerosis. In Chile, both the incidence of multiple sclerosis and the risk of developing it after an acute unilateral or bilateral optic neuropathy, is significantly lower (4.3%).[1] It has been suggested that K and J mitochondrial DNA (mtDNA) haplotypes, characteristic of the European genetic background, might contribute to susceptibility to multiple sclerosis.[2] Research in the genetic epidemiology of cholesterol cholelithiasis among Chileans showed that 88% of Chilean Hispanics harbour Amerindian mtDNA haplotypes.[3]

Clinically isolated BSON is less well understood than AUON. A study conducted in London reported that four out of 23 patients (17%) with BSON had mtDNA mutations related to Leber hereditary optic neuropathy (LHON), and that a similar proportion developed multiple sclerosis.[4] As in multiple sclerosis, mtDNA lineage may have a role in the expression of LHON. Brown *et al* demonstrated the clustering of patients with LHON, especially those with the 14484 mutation, on European haplogroup J.[5]

Three mtDNA point mutations are considered primary mutations for LHON at mtDNA nucleotide positions (np) 3460,11778, and 14484. All of them alter the first enzyme complex of the mitochondrial electron transport chain. Most Native American mtDNAs fall into four distinct haplotypes (A-D). Given that in our population the mtDNA background is predominantly Amerindian and that we have a low incidence of multiple sclerosis developing after optic neuropathy, we studied the primary LHON mtDNA mutations and the mtDNA haplotype in Chilean patients with unexplained AUON or BSON.

Patients who had a history of toxin exposure, alcohol and tobacco misuse, evidence of a generalised demyelinating disease, CNS infections, collagen vascular disorders, increased vascularity around the optic disc at presentation, or family history of optic neuropathy were excluded. The same criteria were used in Morrisey *et al*.[4] We identified 58 patients. The ethics committee of the Hospital Clínico de la Universidad Católica de Chile approved the study. Total DNA was extracted from peripheral blood samples. Polymerase chain reaction (PCR) amplification and RFLP analysis evaluated the presence of the primary mutations at np 3460, 11 778, and 14 484. The mtDNA genotype analysis was performed similarly.

All Native American mtDNAs cluster into one of four distinct lineages, defined by restriction site variants: group A, defined by an *Hae*III site gain at np 663; group B by a nine base pair (9 bp) COII-tRNA^{Lys} intergenic deletion; group C by a *Hinc*II site loss at np 13 259, and group D by an *Alu*I site loss at np 5176.

There were 27 men and 31 women. Fourteen had AUON and 44 had BSON. The mean age at onset of AUON was 31.2 years (range 12–52) and of BSON 30.2 years (range 7–64). Seven males and one female had the mtDNA mutation at np 11 778. One male had the np 14 484 mutation (table 1). We did not find the np 3460 mutation. All the patients with mtDNA mutations had BSON. Most of the patients with BSON had a native American mtDNA haplotype (79%). The number was smaller for the AUON (56%). The nine patients with BSON carrying mtDNA mutations belonged to the D group of Native American mtDNA.

The longest duration of follow up for AUON was 36 months and for BSON 48 months. None of these patients had developed multiple sclerosis during this period of observation.

Our results are interesting in three main areas: pathogenicity of the primary LHON mtDNA mutations, mtDNA background as modulating factor for disease expression, and causes of BSON.

We found patients with BSON carrying the mtDNA np 11 778 and 14 484 mutations. All of them had a native American mtDNA haplotype. This confirms the pathogenicity of both mutations as they are related to disease in a different mtDNA background, extends it to the Native American mtDNA, and suggests that this mutation has arisen independently in several mtDNA lineages. We did not find any patient with the mtDNA 3460 mutation. There are several possible explanations. Among them, the 3460 may have not occurred in the Native American mtDNA lineages, or its clinical expression might depend in the presence of an unknown secondary mutation. It also could be due to the small sample size.

It was proposed that in the European white population, the mtDNA haplotype J plays a role in the expression of both 14 484 and 11 778 mutations, as they show a strong preferential association with that haplotype.[5] Interestingly, all the patients in our study in whom a BSON was related to a primary mtDNA mutation belonged to the haplotype D. In our aboriginal population the D haplotype is predominant (47%), and this figure likely represents the general population with Hispanic last names, but this needs to be formally ascertained. We found an absolute predominance of the D haplotype among our patients with mtDNA mutations, which could be due to a founder effect. It is possible that this haplotype promotes mtDNA related optic neuropathy. Further work is needed to better define the proportion of the different mtDNA lineages in the Chilean population.

Nine out of 44 (21%) patients with BSON had LHON based on carrying mtDNA mutations characteristic of the disease. This number is similar to what was reported in the English study,[4] and therefore stresses the need to test for these mutations in BSON. We do not have a longer follow up to rule out multiple sclerosis with certainty, as the cause for the disease in some of our patients. It is unlikely though, as we know that this is an uncommon evolution in our patients with optic neuropathy.[1] We did not find the primary mtDNA mutation related to LHON in any of 14 patients with unexplained AUON. Although LHON is classically bilateral, these patients were investigated due to the particular natural history of AUON in Chileans and because we knew that they most likely had an Amerindian mtDNA lineage. Studies of additional patients should clarify the role of mtDNA mutations in AUON.

Table 1 mtDNA mutations and haplotypes in Chilean patients with optic neuropathy

Patient	*Sex*	*Age*	*Visual acuity*	*mtDNA mutation*	*MtDNA haplotype*
1	M	29	fc/fc	11778	D
2	M	38	fc/0.05	11778	D
3	M	35	0.05/0.05	11778	D
4	M	28	fc/fc	11778	D
5	F	33	0.05/0.05	11778	D
6	M	35	0.1/0.1	14484	D
7	M	24	0.05/fc	11778	D
8	M	17	0.05/0.05	11778	D
9	M	42	fc/fc	11778	D

fc=finger count.
Only the positive patients for mtDNA mutations are shown.

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CORRESPONDENCE

Dementia as a complication of schizophrenia

De Vries *et al*[1] suggested that dementia in schizophrenia seems to be a real entity with neuropsychological signature similar to that of frontotemporal dementia. This was based on clinical data in eight patients with chronic schizophrenia aged 28 to 64 years presenting with cognitive impairment and evidence of a dementia syndrome not sufficiently explained