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 Morrissey *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^{3'} 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.

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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.

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

by their schizophrenic symptoms. However, except for frontal or temporal hypoperfusion on SPECT, they found no characteristic structural imaging abnormalities and, in accordance with Harrison,² concluded that dementia in elderly schizophrenic patients shows no evidence of any known neurodegenerative disorder and, therefore, requires novel neuropathological explanation. Several recent postmortem studies on such patients showed no excess of Alzheimer's disease or other organic dementing syndromes. This is in line with a personal retrospective study of 99 consecutive necropsy cases of schizophrenic patients aged over 55 (mean age 69.5 (SD 8.25) years) with mean duration of illness of 35.15 (SD 10.1) years, 56% with clinical signs of moderate to severe dementia, where we found a total incidence of definite and probable Alzheimer's disease (using CERAD criteria and Braak staging) of 7.1%, or of 8.7% for those over the age of 65 years. In addition, there was one case each with multi-infarct encephalopathy and Parkinson's disease pathology, and 11 brains showed a lacunary state in the basal ganglia.³ Brain weight in demented elderly schizophrenic patients was significantly lower (mean 1119.5 (SD 106.1) g) than in non-demented ones (mean 1216.3 (SD 36.2) g; $p < 0.001$). These data are in line with previous studies showing that cognitive decline in chronic schizophrenic patients seems best related to loss in brain weight, decrease in brain length, and increased ventricular size.^{4,5} However, demented patients in our cohort were significantly older (mean age 73.36 (SD 6.85) v 64.02 (SD 6.54) years; $p < 0.001$), and had a significantly longer duration of illness (mean 41.1 v 28.9 years; $p < 0.001$), suggesting a progressive cognitive decline with both age and duration of the disorder. This, at least in part, could be explained by recent studies demonstrating reduction of synaptophysin (a synaptic plasma membrane protein) immunoreactivity in the prefrontal cortex⁶ and significant negative correlations between age and concentrations of synaptic plasma membrane proteins and syntax in mRNA in the temporal cortex of schizophrenic patients⁷ reflecting abnormalities in synaptic connectivity; this may cause functional impairment of the limbic circuitry that is thought to be central in the integration of behaviour and cognition.³ These findings are consistent with the hypothesis that changes in synaptic function in both prefrontal or limbic circuits in patients with chronic schizophrenia may contribute to the pathophysiology including cognitive dysfunctions in this disorder.^{3,7,8} However, future prospective clinicopathological and molecular genetic studies using validated methods are necessary to elucidate the bases of cognitive impairment and dementia in chronic schizophrenic patients.

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The calcified intracorporeal vacuole: an aid to the pathological diagnosis of solitary cerebral cysticercus granulomas

I read with interest the paper by Chacko *et al* reporting the significance of calcified intracorporeal vacuole: an aid to the pathological diagnosis of solitary cysticercus granulomas.¹ I appreciate the efforts of the authors for once again proving that the aetiology for single small enhancing CT lesions is neurocysticercosis. The investigators are right in stating that in 26 patients there was no evidence of tuberculosis or fungal pathology. The presence of histiocytes and eosinophils favour a parasitic aetiology. It would be of interest to know the radiological correlation of oval calcified bodies that were detected in six patients. Did they have type A or type B lesions? The authors, in their earlier study, had concluded that neither the duration of seizures nor the type of lesion on CT was predictive of the presence of the parasite in the granuloma.² I am keen to know the seizure control of these patients with oval calcified bodies, as the authors have stated that a small proportion of study patients had intractable epilepsy. Single small enhancing CT lesions are reported to be the cause of the seizure in 26% of Indian patients who present with partial seizures. Cysticercus granulomas and tuberculomas are the two common differential diagnoses that are considered in a patient with seizures and solitary enhancing lesion on CT.³ The authors have demonstrated very well the aetiology, diagnosis, and management of single small enhancing CT lesions in their previous studies.³⁻⁴ This study adds one more feather to their cap in confirming the aetiology of such lesions. It is heartening to see that general practitioners, physicians, and even neurologists in this part of the country treat these patients with antituberculous drugs. Educating general practitioners and general physicians about the nature and aetiology of these lesions will definitely improve the management of patients.

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Chacko replies:

All six patients with oval calcified bodies had type A lesions, of which two were ring lesions and four were discs.

Follow up of 6 months to 3 years is available for four of these patients and they are all seizure free, with three of them still on antiepileptic medication.

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Change in oxcarbazepine (Trileptal®) formulation is associated with more side effects and higher blood concentrations

In an *editorial*, Marson and Chadwick review some of the evidence for the effectiveness and tolerability of new drug treatments for epilepsy.¹ They discuss the role of randomised clinical trials for providing data that satisfy the requirements of the licensing bodies but that do not reflect day to day clinical practice. With oxcarbazepine (Trileptal®) we recently experienced another complicating factor, a change in formulation, which may influence interpretation of results of clinical trials.

Oxcarbazepine had recently been licensed in the United Kingdom and the United States but was already registered in The Netherlands in 1991. In our epilepsy centre we have had extensive clinical experience with oxcarbazepine since 1986.² In 2001 we noticed new symptoms such as diplopia, dizziness, dysarthria, and ataxia in patients on a stable drug regimen, including oxcarbazepine. These symptoms had a fluctuating course during the day. In the autumn of 2000 the manufacturer Novartis substituted the formulation of oxcarbazepine in The Netherlands for the formulation which had been licensed in the United Kingdom and the United States. Taking into consideration this change in formulation we hypothesise that these new symptoms could be side effects of oxcarbazepine, probably caused by higher blood concentrations of the active compound in relation to this new formulation.

Oxcarbazepine is a 10-keto analogue of carbamazepine (CBZ) with similar anticonvulsant efficacy, but with a different pharmacokinetic profile and possibly a better tolerability.^{3,4} It is rapidly reduced to a 10-monohydroxy derivative (MHD) with an elimination half life of 1.3-3.8 hours. Oxcarbazepine acts as a prodrug of MHD, the clinically relevant metabolite of oxcarbazepine; MHD is cleared with a half life of 8.8-24.5 hours.

We evaluated steady state oxcarbazepine and MHD serum concentrations obtained before and after change of the oxcarbazepine formulation from four patients with presumed side effects. The mean (range) MHD concentrations increased from 27.0 (25.4-32.7) $\mu\text{g/ml}$ to 38.4 (37.5-39.6) $\mu\text{g/ml}$. Routinely, we do not measure oxcarbazepine concentrations, because they are usually very low or not detectable. As we still had all serum samples from these four