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SHORT REPORT

mtDNA haplogroup J: a contributing factor of optic neuritis

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Optic neuritis frequently occurs in multiple sclerosis (MS), and shares several similarities with the optic neuritis of Leber's hereditary optic neuropathy (LHON), which is mainly due to maternally transmitted mitochondrial DNA (mtDNA) mutations. Our report shows for the first time that a mitochondrial DNA background could influence the clinical expression of MS. One European mtDNA haplogroup was found only in MS patients with optic neuritis but not in MS patients without visual symptoms. Therefore, we hypothesize that mtDNA haplogroup J might constitute a risk factor for optic neuritis occurrence when it is coincidentally associated with MS, but not be a risk factor for developing MS *per se* as suggested previously.

Keywords: multiple sclerosis; optic neuritis; LHON; mtDNA; haplotypes

Introduction

In respect of LHON, the mtDNA 'primary' mutations alone can lead to optic atrophy, but several 'secondary' mitochondrial mutations must be associated to induce clinical expression of LHON.[1] Torroni *et al* have recently shown that phenotypic expression of some primary mutations (at position 11778 and 14484 of the mtDNA) is greatly influenced by mtDNA background.[2] Several mitochondrial haplotypes are found in human populations, most of them being determined by homoplasmic secondary mutations which are usually found in normal populations.[3] Among the nine European mitochondrial DNA clusters identified, the haplogroup J is found in 2–14% of European populations. This haplogroup J is characterised by the presence of two mutations at the nucleotide positions 4216 and 13708.[2] Additional mutation at position 15257 provides the haplogroup J2. Torroni *et al* have shown that haplogroup J increases the risk of disease expression when a primary mutation is present. Haplogroup T is characterised by the association of 4216 and 4917 point mutations. This haplogroup does not contribute to phenotypic expression of LHON.[2]

Multiple sclerosis (MS) is a multifactorial disease involving both genetic[4] and environmental factors.[5] Since 1964, several authors have reported clinical associations of MS with Leber's hereditary optic neuropathy.[6–9] A link between mtDNA mutations and MS had been postulated previously but remained controversial.[10] The prevalence of mtDNA mutations in MS patients versus controls has been studied by several groups. Mayr-Wohlfart *et al* showed a greater prevalence of associated mtDNA secondary mutations in a group of patients with severe optic involvement than in controls.[11] They suggested that these mutations were a risk factor for developing MS with optic neuritis. Kellar-Wood *et al* did not find any link between mtDNA mutations and a large group of MS patients.[12]

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Hanefeld *et al* reported a greater prevalence of mtDNA mutations 4216 and 4917 in childhood MS versus controls but no greater prevalence for the 13708 mutation in the affected group of patients.[13] Kalman *et al* showed an increased incidence of secondary mutations not necessarily associated with optic involvement.[14] But, to our knowledge, no one has yet compared the mutation prevalence in two subgroups of MS patients (with and without optic involvement) in order to see if the ocular expression of the disease, and not the disease itself, was influenced by mtDNA.

Patients and Methods

Fifty Caucasian unrelated patients with MS as defined by the Poser criteria[15] and 50 controls (matched by age, gender and ethnic distribution) were studied. All individuals gave their consent for this study. The groups of patients with or without optic neuropathy story (25 patients each) were defined clinically (transitory vision loss story, visual acuity evaluation).

mtDNA mutations analysis at nucleotide positions T4216C, A4917G, G13708A, G15257A and G15812A was performed as described by PCR-restriction methods, and all detected mutations were confirmed by sequencing.[11,14]

Statistical analysis was performed using an exact Fisher's test to compare differences between the two groups of patients. A difference was considered statistically significant if $P \leqslant 0.05$.

Results and Discussion

We studied the mtDNA of 50 patients affected by multiple sclerosis with (25 patients) or without (25 patients) a history of clinical optic neuropathy, versus 50 controls not affected by any neurological diseases. Results are shown in Table 1. The haplogroup J was found in 5/50 patients (10%) (four patients with haplogroup J and one with haplogroup J2), and in 5/50 controls (10%) according to prevalence in Europe.[2] Surprisingly, the five patients carrying the haplogroup J (4216 and 13708 associated mutations) were all found in the optic neuropathy group ($P = 0.05$), and in four of them it was the initial symptom. Moreover, one patient with a history of optic neuritis had the single mutation 13708 not associated with the 4216 mutation (European haplogroup X).[2] If 24% (6/25) of patients with optic neuritis had the 13708 mutation associated with optic symptoms, then none of the patients unaffected by optic neuropathy had haplogroup J or 13708 mutation alone ($P = 0.02$). The haplogroup T (association of 4216 and 4917 mutations) was found in 4/50 (8%) patients (1/25 in the optic involvement group and 3/25 in the group without visual expression) and in 6/50 (12%) controls.

There is clear evidence that haplogroup J is not predominant in MS, as it has been proposed. But it predominates widely in the subgroup of patients affected by optic neuropathy and is absent in the subgroup of patients without visual expression. Indeed, haplogroup J could be a genetic factor of visual impairment which could be useful for monitoring people affected by multiple sclerosis. These results are preliminary and must be confirmed by increasing the size of the groups. Moreover, it will be interesting to see if the haplogroup J is also associated with other forms of optic neuropathy (eg in alcoholic optic neuropathy).

Our results emphasise the possible complementary effects of different alleles in the occurrence of a specific tissue expression of a multigenic disease.[4] However, better knowledge of the composition of mtDNA is necessary to understand pathogenic mechanisms. A deleterious factor could be due either to mutation at position 13708, or to unknown mutations carried by haplogroup J. As suggested by Wallace,[1] some mtDNA mutations could lower the tissue-specific energetic thresholds in mitochondrial diseases and aging. Our

Table 1 MtDNA haplotypes and mutations in controls and in two subgroups of MS patients

	mtDNA mutations			*mtDNA haplotype*		
	4216	*4917*	*13708*	*J*	*X*	*T*
controls (50)	11 (22%)	6 (12%)	5 (10%)	5 (10%)	0 (0%)	6 (12%)
total MS (50)	9 (18%)	4 (8%)	6 (12%)	5 (10%)	1 (2%)	4 (8%)
MS with ON (25)	6 (24%)	1 (4%)	6 (24%)	5 (20%)	1 (4%)	1 (4%)
MS without ON (25)	3 (12%)	3 (12%)	0 (0%)	0 (0%)	0 (0%)	3 (12%)

Haplotypes: J (4216+13708), X (13708 alone), and T (4216+4917). ON: optic neuritis.

results suggest a similar pathogenic effect of haplogroup J on visual expression threshold in MS.

In conclusion, we propose that mitochondrial haplotype may influence the phenotypic expression of the multiple sclerosis but not the occurrence of the disease itself. Our finding could reconcile the apparently contradictory results previously published on putative implication of mitochondrial DNA in MS. Indeed, ocular expression of LHON and MS could be influenced by the same mitochondrial genetics factors. We are now evaluating this hypothesis in a larger study, in order to confirm its statistical significance.

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