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Original article

Leber hereditary optic neuropathy in the population of Serbia

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ABSTRACT

Background: Leber hereditary optic neuropathy (LHON) is the most common mitochondrial disorder. However, few countries have published their population-based findings related to this multisystemic disease.
The aim: In order to get a better insight into the epidemiological and clinical picture of this maternally inherited disorder, we performed the first population-based clinical and molecular-genetic study of LHON in the Serbian population.
Methods: Prospective study included patients who were diagnosed with LHON after detailed medical examination and molecular-genetic confirmation.
Results: We identified 41 individuals from 12 genealogically unrelated families, carrying one of the three "primary" mitochondrial (mt) DNA point mutations associated with LHON. Fourteen of them were clinically affected, giving a minimum point prevalence of 1.9 per 1 000 000. The minimum point prevalence for mtDNA LHON mutations was 5.2 per 1 000 000. Male to female ratio was 6:1. Only one affected patient harboured mutant mtDNA in heteroplasmic condition. All patients were presented with common clinical findings.
Conclusion: We observed significantly lower prevalence and higher gender ratio than expected. However, frequencies of primary mutations, incidence of heteroplasmy and clinical findings are in accordance with other studies in Caucasoid populations. Our results might be a consequence of poor recognition and misdiagnosis due to lack of diagnostic possibilities of the entity in different region of our country or less likely be in part due to specific haplotype background of Serbian population which should be further investigated.

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1. Introduction

Leber hereditary optic neuropathy (LHON, MIM 535000), the most common mitochondrial disorder, is characterized by acute or subacute painless loss of central vision, usually in young adults, predominantly male.[1,2] Apart from visual loss as its distinctive feature, LHON may be associated with other neurological, cardiac and skeletal abnormalities, characterizing the "LHON plus" phenotype.[2] This maternally inherited disorder is mainly associated with mitochondrial DNA (mtDNA) mutations 11778G>A, 3460G>A and 14484T>C, all involving genes encoding complex I subunits of mitochondrial respiratory chain.[3]

The median age of onset in LHON is between 15 and 35 years, but an individual can become affected at any age between 2 and 80.[4–7] A few reports found a bit later age of onset in females.[8,9]

The disease usually presents with a loss of central vision involving first one eye and then the other with a mean interval of 2 months (75% of cases).[10] The fellow eye can also be affected simultaneously (25%) or very rarely the disease can remain monocular.[8,10,11] LHON is acute or subacute, but may also manifest as slowly progressive visual loss. Visual impairment is usually severe with visual acuity ranging from 20/200 to counting fingers, in association with profound dyschromatopsia, centrocaecal scotomas and relative preservation of peripheral visual field and pupillary reflexes.[12,13] Following the acute phase, on average within six weeks from the disease onset, the optic disc becomes atrophic. Significant improvements in visual acuity are rare and in most individuals vision remains severely impaired.

The clinical diagnosis is based on the ophthalmologic features and molecular-genetic testing. Relevant testing may include fundus examination (to identify the characteristic optic disc and vascular changes), kinetic (Goldman) or static perimetry (for central or centrocaecal scotoma), electrophysiological studies in selected cases (visual evoked potentials and pattern electroretinogram), optical coherence tomography (to assess the retinal nerve fibre layer thickness and the optic nerve anatomy) and neuroimaging (to exclude compressive, infiltrative and inflammatory causes of bilateral optic neuropathy).[3]

In order to get a better insight into the epidemiological and clinical picture of LHON, we present the first population-based clinical and molecular study of LHON in the population of Serbia as region of Europe, in particular as part of the West Balkan area.

2. Materials and methods

This prospective study included patients with clinical signs of LHON who were examined and ambulatory monitored in the Clinic of Neurology and Psychiatry for Children and Youth, Clinic of Neurology and Institute of Ophthalmology, Clinical Centre of Serbia, Belgrade in the period of 2000 until February 2013. The study also included family members at risk of developing LHON, being unaffected mutation carriers. The follow-up period was approximately 12 years. The Clinic of Neurology and Psychiatry for Children and Youth in Belgrade is the only referent institution in Serbia where the diagnosis of LHON could be established, therefore it poses the unique database of LHON patients for this region.

Prior to inclusion in the study, thorough history was obtained and pedigree analysis performed and all participants underwent physical, neurological and neuro-ophthalmologic examinations. In addition, we have performed fluorescent angiography (FSA), visual electrophysiology, serum lactate and pyruvate levels, blood levels of thyroid hormones, cerebrospinal fluid analysis and magnetic resonance imaging (MRI) of the brain and optic nerves in order to exclude the other ocular or systemic diseases. Probands and their family members were thoroughly informed about the clinical findings. Those with a clinical diagnosis of LHON and their at-risk asymptomatic family members were advised to have a molecular-genetic testing to rule in or rule out the diagnosis. Having obtained their informed written consent, molecular-genetic tests were performed from venous blood samples (5 ml) in the Laboratory of Neurogenetics, Department of Neurological Sciences, Bologna, Italy and the Laboratory of Neurogenetics in the Clinic of Neurology, Clinical Centre of Serbia, Belgrade. The inclusion criteria were having primary (11778, 3460 and 14484) or secondary (14495, 14482, 10663) mtDNA LHON-causing mutations. Local ethical committee approved the research protocol according to the national regulations and study was performed in accordance to ethical standards of the Declaration of Helsinki.

3. Results

During a 12 year follow-up period we identified 41 individuals, from 12 genealogically unrelated families, carrying mitochondrial DNA mutations associated with LHON. Fourteen of them were clinically affected (probands), giving a minimum point prevalence of 1.9 per 1 000 000.

All of the 12 Serbian LHON families harboured a primary mutation. This makes the minimum point prevalence of LHON mutations 5.2 per 1 000 000. Mutations were distributed as follows: MT-11778/ND4 – 58.5% (9/14), MT-3460/ND1 – 34.2% (4/14) and MT-14484/ND6 – 7.3% (1/14) (Fig. 1).

In the affected group there were 12 (85.7%) male and 2 (14.3%) female subjects. The gender ratio in this group was different depending on the mutation type. The 11778/ND4 mutation was associated with a less prominent gender ratio (7 males and 2 females), while marked male predominance was

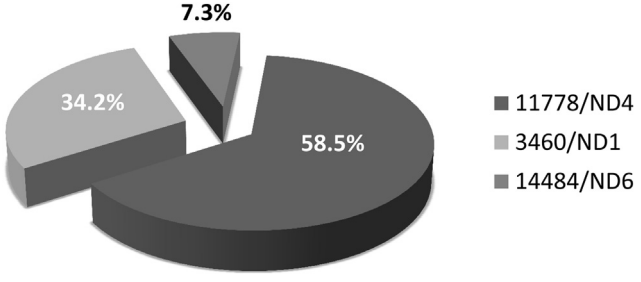

Fig. 1 – The distribution of primary mutations.