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REVIEW

Leber's hereditary optic neuropathy is multiorgan not mono-organ

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Abstract: Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disorder with bilateral loss of central vision primarily due to mitochondrial DNA (mtDNA) mutations in subunits of complex I in the respiratory chain (primary LHON mutations), while other mtDNA mutations can also be causative. Since the first description, it is known that LHON is not restricted to the eyes but is a multisystem disorder additionally involving the central nervous system, ears, endocrinological organs, heart, bone marrow, arteries, kidneys, or the peripheral nervous system. Multisystem involvement may start before or after the onset of visual impairment. Involvement of organs other than the eyes may be subclinical depending on age, ethnicity, and possibly the heteroplasmy rate of the responsible primary LHON mutation. Primary LHON mutations may rarely manifest without ocular compromise but with arterial hypertension, various neurodegenerative diseases, or Leigh syndrome. Patients with LHON need to be closely followed up to detect at which point organs other than the eyes become affected. Multiorgan disease in LHON often responds more favorably to symptomatic treatment than the ocular compromise.

Keywords: mitochondrial DNA, heteroplasmy, respiratory chain, LHON, genotype–phenotype correlation

Introduction

Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disorder with bilateral loss of central vision predominantly in young males.[1] Clinically, LHON is characterized by unilateral acute loss of central vision followed by the same event in the fellow eye within a few weeks to months, with disk hyperemia in the acute phase.[2] In ~25% of cases, visual loss may be bilateral at onset. LHON is mainly due to three so-called primary LHON mitochondrial DNA (mtDNA) mutations m.11778G>A, m.3460G>A, and m.14484T>C, localized in the coding regions for ND4, ND1, and ND6 of complex I of the respiratory chain, respectively.[1] Other mtDNA mutations (eg, m.3434T>C, m.3483G>A, m.3635G>A, m.3866T>C, m.9011T>C, m.11253T>C, m.11696G>A, m.13042G>A) have also been reported to cause LHON.[3–6] There is increasing evidence that LHON is not a mono-organ disorder but rather a multiorgan disease with predominant manifestations in the eyes. This review is aimed at summarizing and discussing recent findings concerning the multisystem nature of LHON.

Methods

Data for this review were identified by searching MEDLINE, Current Contents, EMBASE, Web of Science, Web of Knowledge, LILACS, SCOPUS, and Google Scholar for references of relevant articles using the search terms "central nervous

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system", "peripheral nervous system", "endocrine", "cardiac", "gastro-intestinal", "kidney", and "renal", in combination with "mtDNA", "respiratory chain", "mitochondrial disorder", and "LHON". Randomized (blinded or open-label) clinical trials, longitudinal studies, case series, and case reports were considered. Abstracts and reports from meetings were not included. Only articles in English, French, Spanish, Japanese, or German that were published between 1966 and 2015 were included. Relevant papers were studied and discussed for their usefulness to be incorporated in this review.

Results

The ophthalmologic compromise in LHON may be associated with central nervous system (CNS) disease,[7] otologic disease,[8] endocrinologic disease,[9] cardiac disease,[10,11] bone marrow abnormalities,[12] vascular disease,[13] kidney disease,[14] or peripheral nervous system (PNS) disease.[15] CNS disease in LHON includes myoclonic epilepsy,[7,16] temporal lobe epilepsy,[17] leukoencephalopathy mimicking multiple sclerosis,[18] psychomotor regression,[1] posterior reversible encephalopathy syndrome,[19] migraine with or without aura,[16,20] chorea,[21] cerebellar ataxia,[22] or dementia.[21] Otologic disease in LHON includes hypoacusis or hearing loss.[8,23] Endocrine involvement in LHON may manifest as diabetes,[9] pituitary adenoma,[24] Hashimoto hypothyroidism,[18] or hyperthyroidism.[25] Cardiac involvement in LHON can manifest as left ventricular hypertrabeculation/non-compaction, an unclassified cardiomyopathy characterized by a bilayered structure of the left ventricular myocardium with a spongy inner layer and a compacted outer layer,[10] dilated cardiomyopathy,[11] arrhythmias,[26–28] syncope,[29] palpitations,[29] angina,[29] exertional dyspnea,[29] or sudden cardiac death.[30] Vascular involvement in LHON can manifest as aortic stiffness[13] and bone marrow abnormalities as anemia.[12] Affection of the PNS in LHON can manifest as myopathy, muscle cramps,[16] or demyelinating polyneuropathy.[15] Involvement of the kidneys has been only rarely reported and can manifest as chronic renal failure.[14] A few patients with LHON and neuromyelitis optica and LHON and fibrous dysplasia of the bones have been reported. Some tissues may be subclinically affected, such as fibroblasts[31] or the muscle.[1] The non-ophthalmologic manifestations in LHON may manifest before or after the occurrence of optic atrophy. Some patients with LHON have been reported in whom in addition to optic atrophy, other ocular manifestations were present, such as increased ocular pressure,[32] retinopathy, and cataract.[5]

Discussion

LHON was first described by von Graefe[33] in 1848 and later by Leber[34] in 1871. Already Leber himself reported that some of his LHON patients presented with headache, vertigo, epilepsy, mental impairment, nystagmus, tremor, areflexia, loss of sphincter control, pyramidal tract disease, ataxia, or sensory disturbances.[35] Further evidence was provided later for the fact that LHON is not exclusively an ophthalmologic disorder but rather a multisystem disease with predominant affection of the eyes (mitochondrial multiorgan disorder syndrome).[36,37] There are also indications that primary LHON mutations may not manifest phenotypically with ophthalmologic disease but with dominant organ involvement other than the eyes.[30,38,39] Patients carrying LHON mutations but without optic neuropathy may present with arterial hypertension,[30] different neurodegenerative disease,[38] or Leigh syndrome.[39]

Though it is evident that multisystem involvement can occur in LHON, most of the abnormalities were reported in case reports only. "Absence" of the multisystem nature of LHON may have several reasons. First, most patients with LHON reported in the literature were not systematically and prospectively investigated for involvement of other organs. Second, affection of organs other than the eyes is often subclinical and can be confirmed only by histological investigations. Third, multisystem involvement in LHON is often age-dependent, and hence these patients require regular follow-up investigations not to miss the point at which organs other than the eyes become clinically affected. Fourth, affection of organs other than the eyes is not regarded as part of the LHON phenotype. This can be due to unawareness of the nature of the disease, due to mis-presentation of LHON as a mono-organ problem in the literature, or due to attribution of non-ocular manifestations to causes other than the LHON mutations.

The degree of multisystem involvement appears to depend on various factors such as the patient's age and the type of the underlying LHON mutation. Additionally, there seem to be ethnic differences concerning the variability of the phenotype,[40] since in Thai LHON patients, the male/female ratio is lower and the prevalence of some LHON mutations is higher than that in other ethnic groups.[40] Additionally, the prevalence of primary LHON mutations is particularly low in northern Finland.[41] It is also conceivable that secondary LHON mutations may determine or modify the phenotype. Another factor influencing the phenotypic variability of LHON could be the heteroplasmy rate. Though primary LHON mutations are regarded as homoplasmic,

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there are several indications that they are heteroplasmic in organs other than the eyes. Furthermore, heteroplasmy rates of primary LHON mutations are not 100% in all patients.[42,43] For clinical manifestations of LHON, however, a heteroplasmy rate of at least 60% is required. The lower the heteroplasmy rate, the higher the chance for spontaneous recovery of the ophthalmologic compromise.[44] The lower the heteroplasmy rate in carriers of the disease, the more likely the carrier remains unaffected.[45] A further factor influencing the LHON phenotype is penetrance of the mutations. Only ~50% of male and only 10% of female mutation carriers lose vision. Penetrance can vary markedly in different branches of the same family and between families harboring the same LHON-causing mtDNA pathogenic variants. Several modulators of LHON penetrance have been discussed, such as the mtDNA background haplotypes, ill-defined nuclear DNA background modifiers, environmental factors, such as tobacco smoking and alcohol, and epigenetic factors, such as estrogen hormones. Thus, each of the LHON mutations seems to have a different phenotypic spectrum. Whether all patients with multisystem disease but without an ocular problem should be investigated for primary LHON mutations remains questionable.

Conclusion

This review shows that LHON can be a multiorgan disorder, that involvement of organs other than the eye may be subclinical possibly depending on the heteroplasmy rates of the responsible primary LHON mutation or other modulators, that primary LHON mutations may rarely manifest without ocular compromise, and that LHON patients need to be closely followed up to detect at which point organs other than the eyes become affected.

Disclosure

The authors report no conflicts of interest in this work.

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