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REVIEW

A Comprehensive Review of Leber Hereditary Optic Neuropathy and Its Association with Multiple Sclerosis-Like Phenotypes Known as Harding's Disease

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Abstract: Leber Hereditary Optic Neuropathy (LHON) stands as a distinctive maternally inherited mitochondrial disorder marked by painless, subacute central vision loss, primarily affecting young males. This review covers the possible relationship between LHON and multiple sclerosis (MS), covering genetic mutations, clinical presentations, imaging findings, and treatment options. LHON is associated with mutations in mitochondrial DNA (mtDNA), notably m.11778G>A, m.3460G>A, and m.14484T>C, affecting complex I subunits. Beyond ocular manifestations, LHON can go beyond the eye into a multi-systemic disorder, showcasing extraocular abnormalities. Clinical presentations, varying in gender prevalence and outcomes, underscore the nature of mitochondrial optic neuropathies. Hypotheses exploring the connection between LHON and MS encompass mitochondrial DNA mutations triggering neurological diseases, immunologically mediated responses inducing demyelination, and the possibility of coincidental diseases. The research on mtDNA mutations among MS patients sheds light on potential associations with specific clinical subgroups, offering a unique perspective into the broader landscape of MS. Imaging findings, ranging from white matter alterations to cerebrospinal fluid biomarkers, further emphasize shared pathological processes between LHON-MS and classical MS. This comprehensive review contributes to the understanding of the complex relationship between LHON and MS.

Keywords: visual impairment, mitochondrial DNA, demyelination diseases, neuro-ophthalmology

Introduction

Leber hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disease that causes painless, subacute loss of central vision due to the degeneration of retinal ganglion cells and their axons, leading to optic atrophy.[1] The epidemiology of LHON varies among different nations and regions. In Japan the prevalence is estimated to be 1 in 50,000.[2] In the United Kingdom, epidemiological genetic studies have indicated a prevalence rate of 1 in 31,000,[3] while Australian data indicate a rate of 1 in 68,000.[4] It primarily affects young adults and predominantly males. Interestingly, at younger than 5 years and older than 45 years, the male-to-female ratio of those becoming affected was approximately 1:1.[5]

LHON is associated with mutations in mitochondrial DNA (mtDNA). The most common mutations are m.11778G>A, m.3460G>A, and m.14484T>C, which are associated with the ND4, ND1, and ND6 genes, respectively.[6] The pathophysiology of LHON involves a cascade of events initiated by these mutations. Impaired energy production within mitochondria creates a convenient environment for external stressors to influence the dynamics of retinal ganglion cells. This influence results in the accumulation of reactive oxygen species, energy deficits, diminished biogenesis, increased mitophagy, and, consequently, the death of ganglion cells.[7] Widening the scope beyond the visual

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system, LHON has been identified as a multi-systemic disease with non-ophthalmologic findings. While the ocular manifestations are the hallmark of LHON, it is noteworthy that affected individuals from LHON can also exhibit various extraocular abnormalities. These additional manifestations encompass both non-neurological features such as cardiac arrhythmias and myopathy, as well as neurological abnormalities including tremors, dementia, movement disorders, peripheral neuropathy, and a clinical presentation resembling multiple sclerosis (MS).[8]

The association of LHON and MS acquired the name "Harding's disease" due to a seminal case series conducted by Harding et al.[9] The article reported eight unrelated women with a familial history of LHON, all presenting with bilateral optic neuropathy. Among these cases, six exhibited neurological manifestations consistent with a diagnosis of MS, while the remaining two manifested isolated optic neuropathy along with white matter lesions evident on imaging. In this review, we comprehensively summarize the latest literature and contribute to the understanding of Harding's Disease.

Clinical Profile

A total of 88 cases of Harding's disease have been reported in the literature. Among these cases, a significant majority, accounting for 62 (70.4%), are females, establishing a Female:Male ratio of 2.38:1 (Table 1). In contrast, the ratio for

Table 1 Summary of the Genetic Mutations of All Reported Cases of Harding's Disease

Study	11778 Mutation	14484 Mutation	3460 Mutation	Other mutations
Vanopdenbosch L et al[12]	2 Females, 1 Male	1 Male	1 Male	N/A
Tran M et al[13]	1 Male	N/A	N/A	N/A
Sun MM et al[14]	N/A	N/A	N/A	14502; 1 Male
Rościszewska-Żukowska I et al[15]	1 Female	N/A	N/A	N/A
Riordan-Eva P et al[16]	2 Females	N/A	N/A	N/A
Riccio PM et al[17]	1 Female	N/A	N/A	N/A
Pfeffer G et al[10]	8 Females, 1 Male	1 Female	2 Females	N/A
Perez F et al[18]	1 Male	N/A	N/A	N/A
Parry-Jones AR et al[19]	N/A	1 Female	N/A	N/A
Olsen NK et al[20]	1 Female	N/A	N/A	N/A
Nikoskelainen EK et al[21]	1 Female	N/A	N/A	12811; 1 Male 13967; 1 Male
Matthews L et al[22]	6 Females, 2 Males	1 Female, 1 Male	1 Female	N/A
Martikainen MH et al[23]	1 Male	N/A	N/A	N/A
Manjunath V et al[24]	1 Female	N/A	N/A	N/A
Lev D et al[25]	N/A	N/A	1 Male	N/A
Leuzzi V et al[26]	1 Male	N/A	N/A	N/A
Lee C et al[27]	1 Male	N/A	N/A	N/A
La Russa A et al[28]	N/A	1 Male	N/A	N/A
Küker W et al[29]	1 Female	N/A	1 Female	N/A
Kovács GG et al[30]	N/A	1 Female	N/A	N/A
Kellar-Wood H et al[31]	1 Female	N/A	2 Females	N/A
Joshi S et al[32]	1 Female	N/A	N/A	N/A
Jansen PH et al[33]	1 Female, 1 Male	N/A	N/A	N/A
Horváth R et al[34]	1 Female	1 Female	N/A	N/A
Holmøy T et al[35]	1 Female	N/A	N/A	N/A
Harding et al[9]	8 Females	N/A	N/A	N/A
Flanigan et al[36]	4 Females, 1 Male	N/A	N/A	N/A
Dandekar SS et al[37]	1 Female	N/A	N/A	N/A
Cleaver J et al[38]	N/A	1 Male	N/A	N/A
Charlmers RM et al[39]	4 Females	N/A	N/A	N/A
Chang M et al[40]	1 Male	N/A	N/A	N/A

(*Continued*)

Table 1 (Continued).

Study	11778 Mutation	14484 Mutation	3460 Mutation	Other mutations
Ceranić B et al[41]	1 Female	N/A	N/A	N/A
Cawley N et al[42]	N/A	N/A	1 Male	N/A
Carrara F et al[43]	1 Male	N/A	N/A	N/A
Buhmann C et al[44]	1 Male	N/A	N/A	N/A
Bhatti MT et al[45]	N/A	1 Male	N/A	N/A
Beckmann Y et al[46]	N/A	1 Male	N/A	14325, 3644; 1 Female 14841; 1 Female 9041; 1 Female 9448; 1 Female

Abbreviation: N/A, Not applicable.

Table 2 Comparison of Vision Loss in LHON, MS and Harding's Disease

Parameter	LHON	MS	Harding's disease
Female to Male Ratio	1:3	3:1	2.38:1
Age of Onset	20–30	20–40	30
Vision Loss	May Persists	May recover	May Persists
Laterality of Vision Loss	Mostly sequential with short interval	Mostly Unilateral	Mostly sequential with long interval

LHON is 1:3.[5] This is primarily due to the higher penetrance of the disease in males. The average age of onset of Harding's disease vision loss is 30.5 years.[10] Meanwhile, In LHON, males between 14 and 26 years of age exhibited a striking surge in the onset of vision loss, unlike females who experienced onset across various age ranges without a similar pronounced peak.[5] The onset of visual disturbance in LHON is marked by painless blurring of vision, progressing to a severe loss of visual acuity accompanied by a dense central scotoma. In most instances, both eyes are involved, and the second eye is commonly affected within 6–8 weeks. In the majority of cases, the second eye is involved by one year.[11] Interestingly, in Harding's disease, the pattern, severity of vision loss and the lack of recovery align with those observed in standalone LHON; a unique characteristic of this syndrome is the higher incidence of unilateral visual loss. Additionally, many Harding's disease patients experience more than two visual events, and the time interval before the second eye is affected tends to be more extended compared to classical LHON cases.[10]

Incorporating the fact that the cohort of 56 cases presented by Pfeffer G et al was the largest reported in the literature. Disclosed distinctive characteristics that deviate from the usual profile of LHON. Notably, these cases exhibited multiple episodes of visual loss, a marked predominance among women with a ratio of 19:9, and an extended time interval before the fellow eye was affected, averaging 1.66 years. Interestingly, the majority of patients in this cohort did not report eye pain, and despite being associated with optic neuritis, they demonstrated an unusually poor visual prognosis, a divergence from the anticipated outcomes linked to optic neuritis in the context of MS.[10] In Table 2, a comparison of visual involvement between LHON, MS, and Harding's disease is presented.

Pathophysiology

Several hypotheses have been put forth to establish a connection between LHON and MS.[45] One consideration is that mtDNA mutations, while primarily associated with visual loss, could potentially trigger neurological diseases. However, the expected manifestation of a relapsing-remitting course or paraclinical evidence of demyelinating disease is not anticipated. Another perspective postulates that an immunologically mediated response to mitochondrial genetic products might induce demyelination. Harding et al proposed that the activation of a subset of T cells or circulating antibodies could initiate an autoimmune process, explaining both clinical and paraclinical evidence of demyelination.[9] However, this theory faces a challenge in the lack of concurrent immune diseases in patients with mtDNA mutations. A third

consideration is the possibility that the co-occurrence of the diseases is coincidental. However, this notion has been rejected by Harding et al due to the observed population frequencies of both conditions. It is important to note that at that time, the epidemiology of LHON was not well-defined, and only the m.11778G>A mutation had been identified. Since then, larger studies and the identification of additional mutations (m.14484T>C and m.3460G>A) have expanded our understanding of LHON's prevalence and genetic diversity. Furthermore, technological advancements in neuroimaging have enhanced the ability to study LHON. Despite this, it remains plausible that the predisposition to both diseases is coincidental, with mtDNA mutations potentially influencing the natural history of MS, or vice versa.

There are limited histopathological studies, Kovács GG et al concluded that tissue damage appears to be mediated mainly by T cells and activated macrophages/microglia, with low perivascular inflammatory infiltrates possibly due to immunosuppressant treatment. Additionally, white matter changes are not solely due to multiple sclerosis-like demyelination; vacuolation and diffuse myelin pallor may also contribute. Inflammatory cell presence within LHON lesions is unusual, suggesting early immunological mechanisms alongside optic nerve degeneration. The exact mechanisms behind inflammatory demyelination in LHON are undetermined but may involve mitochondrial dysfunction, autoimmune responses, and molecular mimicry.[30]

Several possibilities emerge to reconcile these conclusions with the distinct phenotype of LHON-MS. One possibility is that mtDNA mutations modify the phenotype of MS, leading to an "atypical optic neuritis" characterized by painless, severe, and irreversible symptoms. Alternatively, genetic, and environmental factors that predispose to MS, particularly enriched in women, may precipitate acute LHON in carriers of mtDNA mutations who would otherwise remain asymptomatic. Another possibility involves a combination of these scenarios, suggesting that having the LHON mtDNA mutation directs an inflammatory response to coincidentally affect the vulnerable anterior visual pathway in individuals already susceptible to developing MS.

Genetic Mutations and Variation

The most prevalent genetic mutation observed in the majority of cases was the 11778 Mutation which was found in 61 out of 88 cases (69.3%), followed by the 14484 and 3460 mutations at rates of 12.5% and 10.2%, respectively. Additionally, there have been reports of other genetic mutations contributing to this complex interplay. A comprehensive summary of the documented LHON-MS cases, along with the associated genetic mutations, is presented in Table 1. The investigation into mtDNA mutations among individuals diagnosed with clinically definite MS has yielded significant insights, as evidenced by various studies. Kellar-Wood et al conducted a comprehensive screening of 307 randomly selected MS patients, revealing an absence of the 11778 or 3460 mutations in the overall population. Nevertheless, when focusing on a subgroup comprising 20 MS patients with early and severe visual loss, the analysis revealed one case harboring the 11778 mutation and two cases with the 3460 mutation.[31] This subgroup analysis highlights the importance of considering specific clinical features in the exploration of mtDNA mutations in MS.

Building on this, Leuzzi et al extended their examination to 74 MS patients characterized by early and prominent optic nerve involvement. Within this cohort, they identified one case with the 11778 mutation.[26] Additionally, Carrara et al further contributed by focusing on 53 MS patients exhibiting severe optic nerve involvement. In their screening efforts, they confirmed the presence of the 11778 mutation in one male patient.[43] This reinforces the notion that mtDNA mutations may play a role in certain subtypes or manifestations of MS, particularly those involving severe optic nerve impairment.

Imaging Findings

On magnetic resonance imaging (MRI), alterations in the white matter within the central nervous system frequently exhibit similarities to the inflammatory demyelinating plaques seen in MS. Lev D et al documentation of anomalous bilateral periventricular white matter spots, resembling inflammatory demyelinating plaques seen in MS.[25] These lesions, characterized by their elongated and perpendicular orientation to the lateral ventricle bodies, with distinct hypointensity in T1 and hyperintensity in T2. Similarities on MRI imaging were noted between LHON-MS and MS according to expert observation. In a study conducted to define MRI features of LMS and LHON, all LHON-MS and MS patients exhibited T2 hyperintense white matter lesion, whereas only 26% of LHON cases exhibited this finding. Notably, 90% of MS

patients and 73% of LHON-MS patients met McDonald's criterion for spatial dissemination. When the images were introduced to blinded radiologists, all LHON-MS and 90% of MS cases were perceived as MS. This observation supports the idea that the observed findings are mostly due to MS related process rather than a distinct Leber process.[22] Kuker et al suggested that LHON-MS may exhibit a distinctive MRI appearance. Lesions in LHON-MS were less bright on T2-weighted images and less visible on T1-weighted images compared to typical MS. Additionally, the distribution of these lesions appeared unique. Periventricular lesions extending along the white matter tracts were noted, along with high signal areas around the anterior horns of the lateral ventricles.[29] This distribution contrasts with the typical Dawson's fingers pattern seen in standard MS.

The case reported by Jaros et al stands out as it explores postmortem histology and revealing T2 hyperintensity in the dorsal spinal tracts of an LHON-MS patient. The identified changes, suggestive of primary spinal cord neurodegeneration potentially linked to mitochondrial dysfunction rather than inflammatory demyelination, introduce a distinctive perspective. This raises questions about the heterogeneity within the LHON-MS spectrum.[47]

Studies have shown that a significant proportion of LHON-MS and MS patients meet the McDonald's criteria for spatial dissemination, and radiologists often misidentify LHON-MS as MS. However, distinct MRI characteristics in LHON-MS contrast with typical MS patterns. Potential variations within the disease spectrum warrants careful consideration in the ongoing exploration of LHON-MS.

Treatment and Screening

The treatment approaches varied widely across studies, encompassing different medications and their combinations with variable effectiveness. Intravenous methylprednisolone was commonly administered in high doses, typically 1 g/day for three days, with some patients experiencing mild improvement in visual acuity.[18] Some patients had moderate improvement and subsequent episodes of vision loss occurred, leading to additional courses of treatment.[28] Plasmapheresis and cyclophosphamide were used, with subjective improvements in light and contrast perception observed in some patients, though these were not consistent across all cases.[18] Mitoxantrone, administered intravenously at doses around 19.2 mg/month, resulted in visual recovery and neurological symptom improvement in some patients, but its severe side effects limited its use.[10]

Idebenone has been explored as a treatment option, showing mixed results. One study noted that it could limit progression in patients with LHON who have discordant visual acuity, with some reports of visual improvement in LHON-MS patients.[10,22,29,33] However, evidence from other cases suggests that while idebenone is safe, its efficacy remains uncertain as it was unable to prevent irreversible blindness in some patients despite increasing the dosage.[18] In some instances, patients' vision continued to deteriorate even with idebenone treatment, although it helped stabilize vision in other cases over a two-year period.[29] The potential of idebenone to limit disease progression and improve visual outcomes, even if only for a subset of patients, is a significant consideration. However, the inconsistency in treatment efficacy cannot be overlooked, suggesting that idebenone may not be a one-size-fits-all solution and that its benefits might be limited. Given these mixed results, a cautious and personalized approach to idebenone use is advisable. It may be beneficial as part of a broader treatment strategy, potentially in combination with other therapies.

Furthermore, other studies have reported positive responses to immunomodulatory drugs, resulting in clinical stability and stable MRI findings. Despite this, treatment did not halt the progression of visual impairment.[15] It appears crucial to maintain immunomodulatory treatment in LHON-MS patients as long as it remains effective, given a report of an inflammatory rebound upon discontinuation of natalizumab.[35]

Several studies have assessed the role of screening for LHON in MS patients. A systematic review and meta-analysis concluded that A total of 1666 patients with MS has been screened for LHON mutations, only 5 patients were identified. Those patients had early and severe course of the disease.[10] Also it is important to note that LHON is not only associated with MS, as there are reports of LHON association with arrythmias,[48] skeletal abnormalities and other neurological pictures such as tremor and dystonia.[21] Screening for LHON mutations in MS patients appears to have a low yield of benefit based on the aforementioned findings. While routine screening may not be justified in all MS patients, targeted screening should be determined on a case-by-case basis.

Limitations

The study has several limitations. Firstly, the rarity of the condition results in a small sample size, which limits the generalizability of the findings. Additionally, the variability in clinical presentations that deviate from the usual profile of LHON. There is also a reliance on historical data and case reports, which may introduce reporting biases. Moreover, the mixed results in treatment efficacy, highlights the need for large-scale, controlled clinical trials to establish standardized treatment protocols. Further longitudinal studies are essential to better understand the disease progression and response to therapies.

Conclusion

This review explores the relation between LHON and MS, highlighting 88 reported cases of Harding's disease, with 70.4% being female, resulting in a Female:Male ratio of 2.38:1. The most prevalent genetic mutation in the majority of cases was the 11778 Mutation (69.3%), followed by the 14484 Mutation (12.5%) and the 3460 Mutation (10.2%). LHON has a higher male predominance with a ratio of 1:3.6 due to greater disease penetrance in males. The average onset age for vision loss in Harding's disease is 30.5 years. In LHON, males typically experience vision loss between 14 and 26 years, while females have a more varied onset age range. Hypotheses linking LHON and MS include mtDNA mutations triggering neurological diseases, immune responses to mitochondrial products causing demyelination, and coincidental co-occurrence of both conditions. Mitochondrial dysfunction, autoimmune responses, and molecular mimicry might explain inflammatory demyelination in LHON. Factors like mtDNA mutations or genetic and environmental predispositions may influence the manifestation and overlap of LHON and MS. MRI imaging of LHON-MS shows similarities to MS, with T2 hyperintense white matter lesions common in both. However, LHON-MS lesions are less bright on T2 and less visible on T1 images, with a unique distribution. Periventricular lesions extend along white matter tracts, differing from typical MS patterns. Postmortem studies suggest primary spinal cord neurodegeneration in LHON-MS, indicating heterogeneity within the spectrum. Treatment for LHON-MS varies widely. Methylprednisolone and mitoxantrone have shown some effectiveness but have limitations due to side effects. Plasmapheresis and cyclophosphamide provided inconsistent improvements. Idebenone showed mixed results, stabilizing vision in some but not preventing blindness in others. Immunomodulatory drugs have maintained clinical stability but did not stop visual decline. Screening MS patients for LHON mutations revealed a low detection rate, suggesting targeted rather than routine screening.

Disclosure

The authors report no conflicts of interest in this work.

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