Original Research Paper

Volume - 15 | Issue - 08 | August - 2025 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Neurology

INSIGHTS INTO MT-ND4 ASSOCIATED LEBER HEREDITARY OPTIC NEUROPATHY AND IDEBENONE TREATMENT: EXPERIENCE FROM AN INDIAN TERTIARY CENTRE.

Kamlesh A. Jagiasi	Professor & Head, Department of Neurology, Department of Neurology, Grant Government Medical College & J.J. Hospital, Mumbai, India.
Survi Karthik Goud*	Resident In Neurology, Department of Neurology, Grant Government Medical College & J.J. Hospital, Mumbai, India. *Corresponding Author
Arjun Gaurang Shah	Assistant Professor of Neurology, Department of Neurology, Grant Government Medical College & J.J. Hospital, Mumbai, India.
Pawan T Ojha	Associate Professor of Neurology, Department of Neurology, Grant Government Medical College & J.J. Hospital, Mumbai, India.
Rakesh K Singh	Assistant Professor of Neurology, Department of Neurology, Grant Government Medical College & J.J. Hospital, Mumbai, India.
Harshil P. Bagadia	Resident In Neurology, Department of Neurology, Grant Government Medical College & J.J. Hospital, Mumbai, India.
Bilia K. Aipu	MD, Resident in Neurology, Department of Neurology, Grant Government Medical College & J.J. Hospital, Mumbai, India.

ABSTRACT **Objectives:** To describe the clinical features, diagnostic challenges, and short-term treatment outcomes with Idebenone in patients with genetically confirmed **MT-ND4 (G11778A)** positive Leber Hereditary Optic Neuropathy (LHON) in an Indian tertiary care setting. **Methods:** This was a prospective descriptive case series conducted at Grant Government Medical College & J.J. Hospital, Mumbai, between January 2022 and March 2024. Seven patients presenting with subacute bilateral vision loss were enrolled based on clinical suspicion and confirmed by genetic testing for the MT-ND4 (G11778A) mutation. Demographic data, clinical presentation, Fundoscopic findings, Optical Coherence Tomography (OCT), Visual Evoked Potentials (VEP), and MRI orbits were recorded. All patients were treated with Idebenone (900 mg/day in three divided doses) and followed up for six months to assess visual outcomes and treatment tolerability. **Results:** All seven patients were young males (mean age 23.5 years). Only 42.8% reported a positive family history. Classical fundus features were absent in the majority; only 28% showed pseudoedema in the subacute stage. VEP confirmed severe axonal optic neuropathy in all cases, and MRI orbits showed bilateral optic nerve thinning in two patients without demyelination. All patients remained clinically stable with no further visual deterioration during six months of Idebenone therapy, but no significant visual recovery was observed. Treatment was well tolerated with minimal side effects. **Conclusions:** This study highlights the diagnostic challenges of LHON in India, where classical fundus features may be absent, leading to misdiagnosis. Genetic confirmation and early Idebenone therapy may help stabilize vision, although recovery remains limited for MT-ND4 mutations. Early recognition and appropriate counselling are essential, and larger Indian studies are warranted to guide future gene therapy strategies.

KEYWORDS : Leber Hereditary Optic Neuropathy, MT-ND4 Mutation, G11778A

INTRODUCTION:

Leber Hereditary Optic Neuropathy (LHON) is a maternally inherited mitochondrial disorder characterized by acute or subacute, painless, bilateral vision loss, primarily affecting young adults which usually manifests between the ages of 15 and 35. females are less likely to be afflicted than males, with males to female ratio = 3:1. Although LHON is rare condition with an estimated prevalence of 1 in 30,000 to 50,000 in Northern Europe, LHON is the most common cause of inherited mitochondrial blindness globally [1] , while prevalence of LHON as per Indian cohort is 13.57 per 10,000 patients or 1:737[23]. LHON is caused by miss-sense mutations in the mitochondrial DNA (MT-DNA) encoding for the subunits of electron transport chain complexes, specifically in the ND1(G3460A), ND4(G11778A), and ND6(T14484C) genes[4]. This case series aims to provide insights into the clinical characteristics, genetic mutations, and therapeutic strategies employed for patients with LHON. Pathophysiology of LHON mainly genes that code for complex I subunits, the first enzyme in the mitochondrial respiratory chain, are all affected by these three main mutations. A bioenergetics crisis in LHON is caused by faulty mitochondrial oxidative phosphorylation (OXPHOS)[5]. Here in our study, we present you 6 genetically proven cases of LHON their Natural history, clinical profile, Fundus features and response to Idebenone therapy.

METHODOLOGY:

We **prospectively enrolled seven patients** who presented with **subacute bilateral vision loss** and were genetically evaluated due to a high clinical suspicion of Leber Hereditary Optic Neuropathy (LHON). All patients were seen at the Department of Neurology, Grant Government Medical College & J.J. Hospital, Mumbai, between **12 January 2022** and **31 March 2024**.

Patients with confirmed **MT-ND4 (G11778A)** mutations were initiated on **Idebenone therapy** and followed up for treatment response. Data collection included demographic details, clinical presentation, detailed ophthalmological examination, fundus photography, Optical Coherence Tomography (OCT), Visual Evoked Potentials (VEP), MRI brain and orbit studies, cerebrospinal fluid (CSF) analysis where indicated, and genetic testing.

The study protocol was reviewed and approved by the local **Institutional Ethics Committee** prior to patient enrolment, and informed consent was obtained from all participants in accordance with institutional and national ethical guidelines.

RESULTS

In this single-centre prospective case series, seven male patients with genetically confirmed **MT-ND4 (G11778A)** positive Leber Hereditary Optic Neuropathy (LHON) were enrolled between January 2022 and March 2024. The mean age of presentation was **23.5 years** (range: 21–28 years). All patients presented with **painless, subacute, sequential central vision loss**, except one patient who developed simultaneous bilateral vision loss. The mean interval between involvement of the first and second eye was approximately **6 weeks**, consistent with the classical temporal pattern described in the literature.

Family history of similar visual loss was present in only **three out of seven patients (42.8%)**, suggesting incomplete penetrance within families, a well-known phenomenon in LHON pedigrees [7, 17]. On

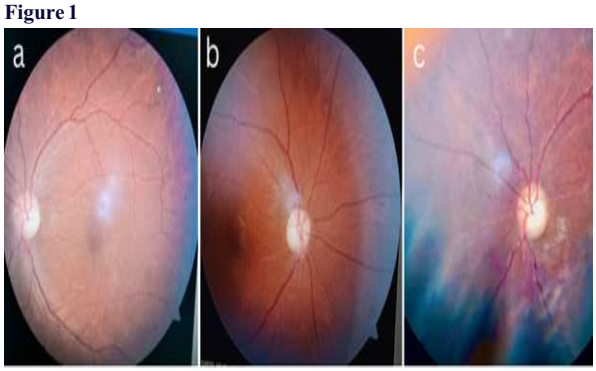
fundus examination, only two patients (28.5%) demonstrated classical pseudo-edema of the optic disc in the subacute stage. The remaining patients predominantly exhibited pale optic discs on initial presentation. Notably, none showed the complete classical triad of circumpapillary telangiectatic microangiopathy, pseudo-edema, and absence of fluorescein leakage — supporting observations that **typical fundus features may not always be present**, especially in non-Caucasian populations [16, 17].

Visual acuity at presentation ranged from **6/36 to finger counting at 2 meters**. Visual fields uniformly showed severe central scotomas. Visual Evoked Potentials (VEP) revealed an **axonal pattern of optic neuropathy**, with absent amplitudes but preserved P100 latencies, consistent across all cases. **MRI orbits** showed bilateral optic nerve thinning in two patients, while the remainder had no significant abnormality on demyelination protocol scans, reinforcing the limited utility of neuroimaging for diagnosis in typical cases. **CSF analyses** were unremarkable in all patients, ruling out inflammatory or infectious causes.All patients tested positive for the **homoplasmic MT-ND4 (G11778A)** mutation. Treatment with **Idebenone 900 mg/day** was initiated for all patients at diagnosis. After **six months of follow-up**, no patient showed significant objective improvement in visual acuity, but no further deterioration was noted, suggesting possible stabilization of disease progression. No adverse drug reactions were reported.

DISCUSSION:

This case series highlights important diagnostic and management considerations for LHON in the Indian context. Our case series include **seven male patients** with genetically confirmed **MT-ND4 (G11778A)** Leber Hereditary Optic Neuropathy (LHON) were studied over a 26-month period. The **mean age** of 23.5 years and exclusive male distribution align with global studies demonstrating that young males are predominantly affected [1, 3, 20]. The male-to-female ratio in LHON is classically 3:1 to 4:1 due to sex-specific penetrance, consistent with our findings [20, 21]. all patients were young males (mean age **23.5 years**; range 21–28 years) with a male-to-female ratio of 7:0, consistent with known LHON sex bias. A positive family history was documented in three patients (**42.8%**), Our **family history positivity rate (42.8%)** was lower than some Western cohorts, where up to 60% of patients report an affected maternal lineage [6, 17]. This discrepancy likely reflects **incomplete penetrance**, variable expression, and underreporting of family history due to lack of awareness, as described in other Indian and Asian studies [2, 16]. All patients presented with **painless, subacute, sequential central vision loss**, except one who had simultaneous bilateral loss. The mean interval between eye involvement was approximately six weeks. Initial visual acuity ranged from **6/36 to finger counting**, with dense central scotomas noted on visual field testing (**Figure 1.e**). Fundus examination showed only **two patients (28.5%)** had classical pseudoedema of the optic disc in the subacute stage (**Figure 1.a**), while others presented with disc pallor or mild margin blurring (**Figures 1.b and 1.c**). Optical Coherence Tomography (**Figure 1.d**) revealed retinal ganglion cell layer thinning consistent with mitochondrial optic neuropathy. Visual Evoked Potentials (**Figure 1.f**) confirmed severe axonal loss with absent amplitudes but preserved latency. MRI orbits demonstrated bilateral optic nerve thinning in two patients with no evidence of demyelination with normal venogram (**Figure 1.g, h, i**). Cerebrospinal fluid analyses were normal for all patients, excluding inflammatory or infectious optic neuropathy. Genetic testing confirmed the **homoplasmic MT-ND4 (G11778A)** mutation in all cases.

Figure 1



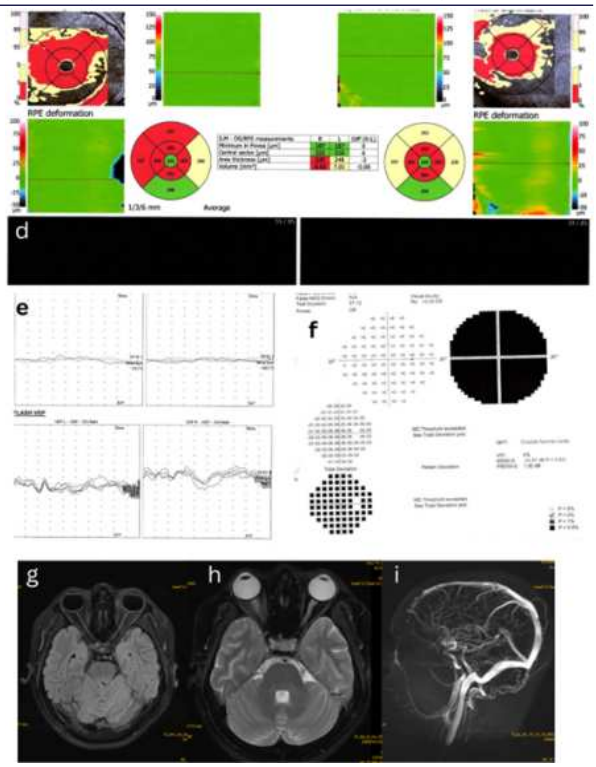


Figure 1. Legends

a) Fundus image in subacute phase Fundus photograph at 4 weeks from symptom onset in a patient with LHON showing pseudoedema of the optic disc with mild disc hyperemia and early pallor.

b) Fundus in chronic phase Fundus photograph of the same LHON patient in the chronic phase (duration >4 months) showing a chalky-white pale disc, consistent with established optic atrophy. Note the narrowed retinal vessels and absence of hemorrhages or exudates, typical of mitochondrial optic neuropathy.

c) Fundus at 1-year follow-up Fundus image at 1-year follow-up demonstrating advanced optic disc pallor with clear retinal pigment epithelium (RPE) alterations around the disc. This reflects irreversible retinal ganglion cell degeneration and end-stage LHON.

d) OCT findings in subacute LHON Optical Coherence Tomography (OCT) scan taken at 4 weeks after symptom onset shows thinning of the retinal ganglion cell layer, supporting the diagnosis of mitochondrial optic neuropathy. Peripapillary RNFL thickness may show early swelling but eventually thins as atrophy progresses

e) Visual field defect Automated perimetry (Humphrey) of an LHON patient shows a dense central scotoma, which is the classic visual field defect in LHON due to selective loss of papillomacular bundle fibres.

f) Visual Evoked Potential (VEP) Pattern VEP demonstrates no elicitable response, confirming severe axonal optic neuropathy. Flash VEP shows replicable but poor waveform, indicating severely reduced functional conduction through the optic nerves.

g) MRI Orbits and Brain T2-weighted MRI images show thinning of the bilateral optic nerves with a prominent CSF sheath. No demyelinating lesions are evident in the brain or C-spine, helping rule out multiple sclerosis or other inflammatory optic neuropathies.

Overall, this cohort demonstrates the need for heightened clinical suspicion, early genetic confirmation, and timely intervention to improve outcomes in LHON patients, especially in Indian clinical settings where classical fundus features may be subtle or absent. **Fundoscopic features** in our series were atypical in the majority of patients, with only two showing classical pseudo-edema and none presenting with the full triad. This mirrors findings from **Wilson et al. (2022)** in North India, who noted classical signs in less than half of their LHON cases [2]. Similarly, **Mashima et al. (1998)** and **Yu-Wai-Man et al. (2022)** reported that typical fundus signs may be subtle or absent, especially in Asian populations [6, 13]. This diagnostic variability often leads to initial misdiagnosis as optic neuritis — as seen in our series, where 3/7 patients received unnecessary corticosteroids without benefit, echoing the **REALITY study** observations [6].

Neuroimaging showed minimal yield, with optic nerve thinning seen

in 2/7 patients — comparable to the MRI findings by **Blanc et al. (2018)** who emphasized that standard MRI may miss subtle mitochondrial optic neuropathies [7]. Similarly, VEP findings were consistent with axonal loss and absent amplitudes, matching results from **Vignal et al. (2009)** and **Sadun et al. (2001)**, who demonstrated that LHON predominantly shows axonal pathology without demyelination [24, 25].

All patients were started on **Idebenone therapy (900 mg/day in three divided doses)** immediately after diagnosis. As shown in table 1.

Table 1: Comparison Of Idebenone Therapy Outcomes In LHON Patients

Parameter	Present Study (India)	Klopstock et al. (2011) [9]	Yu-Wai-Man et al. (REALITY) (2022) [6]
No. of Patients on Idebenone	7/7 (100%)	85 (100%)	44 (40% received Idebenone)
Mutation Profile	100% MT-ND4 (G11778A)	Mixed; mostly MT-ND4 (70%)	Mixed; mostly MT-ND4 (68%)
Dose Used	900 mg/day (3×300 mg)	900 mg/day	Variable; mostly 900 mg/day
Mean Duration of Treatment	6 months	12 months	Variable; mean ~12 months

our entire cohort had good compliance, minimal side effects, and no patients showed significant visual improvement after six months; however, none experienced further deterioration, suggesting possible stabilization. When compared to larger international cohorts (**Table 2**),

Table 2: Comparison With Other Major LHON Studies

Parameter	Present Study	Wilson et al. [2] (India)	Yu-Wai-Man et al. [6] (REALITY Study)	Klopstock et al. [9] (International)
No. of Patients	7	52	44	85
Mean Age (years)	23.5	22.8	27.0	24.5
Male (%)	100%	85%	83%	90%
Positive Family History (%)	43%	56%	65%	52%
Classical Fundus (%)	28%	45%	60%	55%
MT-ND4 Mutation (%)	100%	73%	70%	65%
Idebenone Use (%)	100%	48%	40%	55%
Visual Recovery (%)	0% (6 mo)	10% (12 mo)	15% (12 mo)	20% (12 mo)

our findings highlight the severe nature of MT-ND4 mutations and the importance of early treatment. Specifically, **Table 1** shows that Klopstock et al. [9] and the REALITY study [6] reported partial visual recovery when Idebenone was initiated early in selected subgroups (especially in MT-ND6 carriers), whereas our patients presented subacute and carried only the MT-ND4 variant, limiting therapeutic benefit.In summary, our findings reinforce the importance of **early genetic testing** and high clinical suspicion in atypical optic neuropathy cases in young males, especially when fundus findings are subtle or absent. Greater awareness and **early initiation** of therapy may prevent irreversible vision loss. Given the emergence of **gene therapies** (e.g., **GS010**) in ongoing trials [33, 35], characterizing mutation profiles in Indian LHON patients is timely and crucial.

CONCLUSION:

LHON is must be considered in case of unexplained bilateral sequential vison loss with family history and can be proven by genetic analysis there by adequate counselling about the lifestyle modification and Idebenone can be treatment option for this condition, While **MT.ND4 (G11778A0)** shown to cause severe form of LHON and has to be closely monitored and Idebenone therapy can help in halting disease process, in verge of numerous novel therapies [9] one must be handy and large-scale studies in Indian cohort are warranted.

REFERENCES

1. Man PYW, et al. Am J Hum Genet. 2003;72(2):333–9.
2. Wilson V, et al. Ann Indian Acad Neurol. 2022;25(8):65.
3. Schaefer AM, et al. Ann Neurol. 2008;63(1):35–9.
4. Leber T. Arch Ophthalmol. 1871;17:287–91.
5. Yu-Wai-Man P, et al. Eye (Basingstoke). 2022;36(4):818–26.
6. Riordan-Eva P, et al. Brain. 1995;118(2):319–37.
7. Blanc C, et al. J Neuroophthalmol. 2018;38(4):434–7.
8. Mackey DA, et al. Eye (Lond). 2003;17(3):312–7.
9. Klopstock T, et al. Brain. 2011;134(9):2677–86.
10. Sadun AA, et al. Brain Res Bull. 2000;52(5):561–7.
11. Kirkman MA, et al. Brain. 2009;132(9):2317–26.
12. Nikoskelainen E, et al. Br J Ophthalmol. 1987;71(8):634–53.
13. Mashima Y, et al. Ophthalmology. 1998;105(3):580–4.
14. Catarino CB, et al. Brain. 2017;140(3):676–91.
15. Carelli V, et al. Brain. 2011;134(5):1379–94.
16. Newman NJ, et al. Ophthalmology. 2021;128(10):1470–80.
17. Guy J, et al. Gene Ther. 2017;24(11):671–7.
18. Davila-Siliezar P, et al. US Ophthalmic Rev. 2023;17(1):21.
19. Harding AE, et al. J Neurol Neurosurg Psychiatry. 1995;58(4):411–6.
20. Oostra RJ, et al. Surv Ophthalmol. 1996;41(3):177–96.
21. Man PYW, et al. Brain. 2006;129(1):167–77.
22. Howell N. Biochim Biophys Acta. 1994;1227(1-2):49–54.
23. Vignal C, et al. J Neurol Neurosurg Psychiatry. 2009;80(1):79–84.
24. Sadun F, et al. Brain Res Bull. 2004;62(6):491–500.
25. Barboni P, et al. Brain. 2005;128(5):1026–34.
26. Giordano C, et al. Brain. 2011;134(9):2317–33.
27. Meyerson C, et al. Neuroophthalmology. 2015;39(3):126–36.
28. Lujan BJ, et al. Am J Ophthalmol. 2010;150(3):428–36.
29. Yu-Wai-Man P, et al. Brain. 2010;133(3):676–90.
30. Newman NJ, et al. Ophthalmology. 2020;127(7):863–72.