

LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON): A GLOBAL COMPARISON WITH SPECIAL EMPHASIS ON INDIA**P. Sivabharathi*, V. Vikash, H. Aarthi, K. Madhan, C. Jothimanivannan**

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ABSTRACT

Leber's hereditary optic neuropathy (LHON) is a rare mitochondrial genetic disorder, which is characterized by acute to subacute painless loss of central vision in young adult males. It is caused by a point mutation of mitochondrial DNA, which includes m. 11778G>A, m.3460G>A, m. and m. 14484T>C, resulting in retinal ganglion cell loss due to optic neuropathy. The prevalence of LHON worldwide is considerably variable due to genetic predisposition, geographical factors, and technical factors. In India, LHON is believed to be underdiagnosed and underreported compared to Western and East Asian nations. Also, Limited Availability of physician awareness in LHON can lead to a delay in diagnosis. Data collected in India shows a relatively high prevalence of

sporadic cases and different mutations, of which m. 11778G>a is the predominant mutation. Environmental factors such as alcohol and cigarette use, nutritional deficiencies, and toxic exposures could also affect LHON and impact affected individuals in India. By contrast, the prevalence of better epidemiological data is observed in Japan, China, Europe, and the United States owing to the presence of genetic screening programs and patient registries. Japan has a relatively higher prevalence of m.11778G>A mutations, and European cohorts have a better rate of visual recovery owing to early intervention and treatment with odobenine and novel gene therapies based on adeno-associated virus vectors. In general, though LOHN is a worldwide phenomenon, there are considerable variations between Indian and international cases recording diagnosis, handling, and advancement in research. Enhancement in genetic lab facilities, awareness among doctors, and availability of new treatment are needed for improving the present status of LOHN in India.

KEYWORDS: Mitochondrial Vision Disorder; Maternal Genetic Transmission; Bioenergetic Imbalance; Optic Nerve Neurodegeneration; Selective Retinal Neuron Loss; Mitochondrial Dysfunction–Associated Blindness; Precision Genetic Diagnosis; Neuroprotective Therapeutic Strategies; Inherited Optic Pathology.

INTRODUCTION

Leber's Hereditary Optic Neuropathy (LHON) is a rare, inherited mitochondrial neurodegenerative disease, primarily involving the optic nerve, resulting in acute or subacute central vision loss. LHON was originally described by Theodor Leber in 1871 and is also presently known to be one of the most common forms of primary Mitochondria DNA (mtDNA) Optic neuropathies. LHON usually presents in young adult males, but it can also be presented to anyone of any age and gender. The features of LHON include painless and progressive bilateral blindness, initially monocular and then involving the second eye after weeks and months.

Genetic background of LHON

The genetic background of LHON results from the accumulation of point mutations within the mitochondrial genome. In particular It affects genes that code subunits of enzyme "complex I" of the mitochondrial respiratory chain; "complex I" encodes the "NADH dehydrogenase" enzyme, also known as "NADH: quinone oxidoreductase." Among three major pathogenic variants, "m.11778G>A" encodes "NDH4" subunits; "m.3460G>A" encodes "ND1" subunits; finally, "m.14484T>C" encodes "ND6" subunits.

Retinal ganglion cells (RGC) are particularly sensitive to energy deprivation because of their high energy demand; this renders them particularly susceptible to "mitochondrial."

From a clinical perspective, LHON is characterized by dichromatopsia in the initial stages, central or cecentral scotomas and decreased visual acuity, although the optic disc may remain normal or mildly hyperemic in appearance in the initial stages before developing into optic atrophy. Although many patients are found to carry homoplasmic mitochondria mutations, the fact that not all patients develop visual impairments due to the phenomena of incomplete penetrance and variable expressivity makes this condition very interesting. The role of environmental factors such as smoking, alcohol intake, and exposure to mitochondrial toxins has been suggested to act as triggers for the development of the condition in

genetically predisposed individuals.

From an epidemiological standpoint, LHON affects all populations, regardless of ethnicity, with a prevalence of 1:25,000 to 1:50,000, although there may be underreporting. Advance in molecular genetics have made precise diagnosis much more accurate, allowing for the early assessment of mutation carriers, which has helped in genetic counseling. Moreover, recent advances in therapeutic approaches, which include the use of antioxidants, drug that target mitochondria, such as odobenine, and new approaches in gene therapy by the use of adeno-associated viral vectors, offer hope for his previously untreatable disease. In conclusion, Leber's Hereditary Optic Neuropathy is a paradigmatic mitochondrial disease where dysfunction of energy metabolism translates into a remarkable pattern of selective neuronal damage. The need for basic research on this disease continues to be fundamental not only for advancements in managing affected patients but also for improving our comprehension of mitochondrial pathobiology).

Epidemiology of Leber's Hereditary Optic Neuropathy (LHON)

Leber's Hereditary Optic Neuropathy (LHON) is a rare genetic disorder that affects mitochondria. It mainly impacts young adults and causes sudden or gradual loss of central vision. The disease has unique patterns related to gender, age, genetic background, and geographic location. Global Prevalence LHON is known as a rare disease around the world, with an estimated prevalence of about 1 in 30,000 to 50,000 people. However, the rates differ among various populations due to genetic factors and differences in mitochondrial haplogroups. Higher rates have been observed in European populations, especially in Northern Europe, compared to those in Asia and Africa.

Gender Distribution A notable feature of LHON is its significant male predominance. While the disease is passed down through mothers, 80 to 90 percent of affected individuals are male, and females usually remain carriers without symptoms. This gender difference is believed to be affected by hormonal, genetic, and environmental factors that protect females. Age of Onset LHON usually presents in late adolescence or early adulthood, between 15 and 35 years of age. Cases of childhood and late onset have also been observed, but these are less common. The onset is typically acute, initially involving one eye, followed by the involvement of the second eye weeks to months later.

Geographic and Ethnic Distribution

LHON is a worldwide condition, found in all ethnic groups. The vast majority of LHON are

linked to three major mitochondrial DNA mutations: m.11778G>A, m.14484T>C, and m.3460G>A, which account for nearly 90% of LHON worldwide. Some mutations are more prevalent in specific regions; for instance, m.11778G>A is more prevalent in Asian populations, and m.14484T>C is more commonly found in European populations.

Penetrance and Risk Factors

Carriers of pathogenic mitochondrial DNA mutations do not always express visual symptoms, suggesting that penetrance is incomplete. The penetrance is estimated to be approximately 50% in males and 10% in females. Environmental factors such as smoking, alcohol intake, nutritional deficiencies, and exposure to mitochondrial toxins are thought to increase the likelihood of expression of disease.

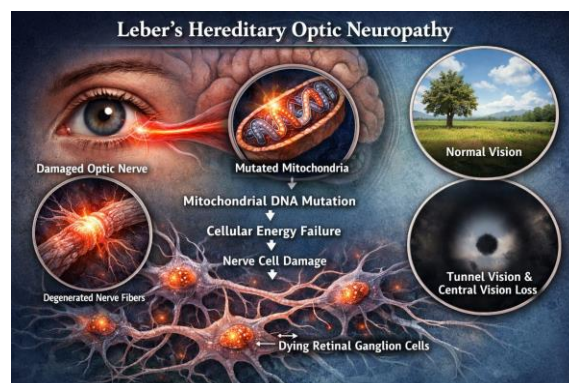
Epidemiology in India

In India, LHON is regarded as an underdiagnosed condition because of the restricted availability of genetic analysis and a lack of awareness. The data accessible indicates that the m.11778G>A mutation is the most prevalent type. The predominance of males and the pattern of onset in young adults, as seen worldwide, is also evident in Indian populations.

Public health care

Despite being rare, the influence of LHON on quality of life, because of the irreversible loss of vision in young, productive individuals, is substantial. Early diagnosis and genetic counseling are essential for at-risk families to minimize preventable environmental factors and enhancement.

GENETIC MUTATION IN LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)



Leber's Hereditary Optic Neuropathy (LHON) is one of the most well-characterized mitochondrial genetic disorders, primarily caused by point mutations in mitochondrial DNA

(mtDNA) that impair oxidative phosphorylation. Unlike Mendelian inherited optic neuropathies, LHON follows maternal inheritance, as mitochondria and their DNA are transmitted exclusively through the oocyte.

Mitochondrial Genetic Basis

Human mitochondrial DNA is a circular genome of 16,569 base pairs encoding 13 proteins essential for the electron transport chain (ETC), particularly oxidative phosphorylation. In LHON, mutations predominantly affect genes coding for Complex I (NADH dehydrogenase) subunits, which play a critical role in ATP production and cellular energy metabolism.

Dysfunction of Complex I leads to

Reduced ATP synthesis
Increased production of reactive oxygen species (ROS)
Oxidative stress–induced apoptosis of retinal ganglion cells (RGCs)
Because RGCs have high energy demands and long axons, they are especially vulnerable to mitochondrial defects.

Primary Pathogenic Mutations

More than 90–95% of LHON cases are attributed to three primary mtDNA mutations:
Mutation Gene.

Complex I Subunit	Clinical Relevance
m.11778G>A MT-ND4	ND4 Most common; poor visual recovery
m.3460G>A MT-ND1	ND1 Intermediate severity
m.14484T>C MT-ND6	ND6 Better visual prognosis
m.11778G>A Mutation	

This mutation in the ND4 gene is the most prevalent worldwide. It causes a structural alteration in Complex I, significantly reducing electron transport efficiency. Patients with this mutation generally have severe vision loss with minimal spontaneous recovery.
m.3460G>A Mutation Located in the ND1 gene, this mutation alters the enzyme's catalytic function and results in moderate mitochondrial dysfunction.
m.14484T>C Mutation.

Affects the ND6 gene and is associated with a comparatively better prognosis and higher rates of visual recovery, especially in younger individuals.

Secondary and Modifier Mutations

In addition to primary mutations, several secondary mtDNA variants may influence disease expression, including:

m.4216T>C

m.13708G>A

m.4917A>G

These mutations alone do not typically cause LHON but may act as genetic modifiers, affecting penetrance and severity.

Homoplasmy and Heteroplasmy

A unique aspect of LHON genetics is the distribution of mutant mtDNA: Homoplasmy: All mitochondrial genomes carry the mutation. Common in LHON but still shows incomplete disease expression. Heteroplasmy: Coexistence of mutant and normal mtDNA. Higher mutant load increases the likelihood of clinical manifestation. This explains variability in disease expression among family members. Incomplete Penetrance and Gender Bias.

Not all mutation carriers develop LHON

~50% of males

~10% of females

develop vision loss.

Genetic explanations include

Nuclear modifier genes that influence mitochondrial function Possible X-linked susceptibility loci Protective effects of estrogen on mitochondrial metabolism.

Mitochondrial Haplogroups

Population-specific mitochondrial haplogroups modulate LHON risk. For example, haplogroup J in European populations has been associated with increased disease expression, likely due to variations that further impair Complex I efficiency.

Gene–Environment Interaction

Genetic predisposition alone is insufficient. Environmental triggers such as smoking, alcohol consumption, and nutritional deficiencies can increase oxidative stress and precipitate visual loss in carriers.

Genetic mutations in LHON primarily involve mtDNA point mutations affecting Complex I subunits, leading to mitochondrial dysfunction and selective retinal ganglion cell degeneration. Disease expression is modified by heteroplasmy levels, nuclear genes, mitochondrial haplogroups, and environmental factors, making LHON a complex interplay between genetics and external influences.

MITOCHONDRIAL HAPLOGROUPS AND ETHNIC INFLUENCE

Role of Mitochondrial Haplogroup and Ethnic Factor in Leber's Hereditary Optic Neuropathy (LHON)

Leber's Hereditary Optic Neuropathy (LHON) is characterized by a high degree of clinical variability despite the known pathogenic mitochondrial DNA (mtDNA) mutations. Not all carriers of disease-causing LHON mutations will suffer from visual impairment, and the severity of the disease also varies greatly among those who are affected. This has resulted in a great deal of research being conducted on the role of mitochondrial haplogroups and ethnic factors as significant modifying variables that affect the penetrance, age of onset, and course of the disease.

Understanding Mitochondrial Haplogroups

Mitochondrial haplogroups are a set of related mitochondrial DNA (mtDNA) sequences that are distinguished by a set of polymorphisms that have been transmitted maternally over thousands of years. These haplogroups have evolved as a result of human migration and adaptation to various environmental conditions. Each haplogroup is linked to minute differences in mitochondrial bioenergetics, such as the efficiency of oxidative phosphorylation, ATP synthesis, and ROS production. In the context of LHON, these naturally occurring mtDNA sequence variations can either exacerbate or mitigate the disease-causing impact of primary LHON mutations, thus making them significant modifiers of the genetic background rather than Asian populations may vary from those found in European populations, and this underlines the significance of ethnic genetic background.

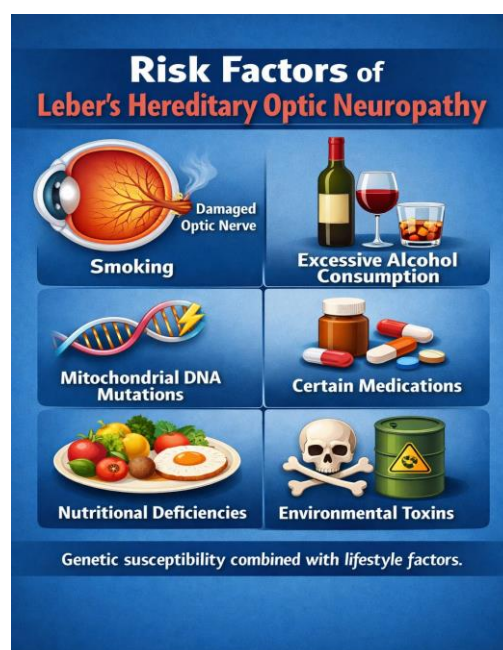
African and Middle Eastern Populations

LHON appears to be a relatively uncommon condition in African populations, even in the presence of primary LHON mutations. The lower penetrance is believed to be affected by the mitochondrial haplogroups that are prevalent in Africa, and these may confer a higher level of resistance to oxidative stress and mitochondrial damage. The data from Middle Eastern populations is sparse but reflects a high degree of genetic heterogeneity. The available evidence suggests that the expression of LHON in these populations may be affected by both haplogroup background and environmental factors, and this underlines the need for further large-scale genetic studies.

Indian Population and South Asian Haplogroups

In the Indian population, LHON remains an underreported and under diagnosed condition. The majority of Indian LHON patients have been found to have the haplogroup M background, which is the most prevalent mitochondrial haplogroup in South Asia. Haplogroup M is extremely diverse and comprises a number of sub-haplogroups that have been shown to have different functional properties. Preliminary data have suggested that their variable pen trace of LHON mutations in Indian families,

RISK FACTORS: LIFESTYLE AND ENVIRONMENT TRIGGERS IN LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)



Nutritional Status and Its Role in Leber's Hereditary Optic Neuropathy (LHON) Although mitochondrial DNA mutations are the key factors in the development of LHON, the nutritional status of the individual is of utmost importance in the manifestation of the disease, the severity of the disease, and the rate of disease progression.

Key Nutritional Factors in LHON

B-Complex Vitamins

Vitamin B12 (Cobalamin) Important in the mitochondrial metabolism of energy and the maintenance of the myelin sheath. Its deficiency may lead to optic neuropathy and exacerbate the manifestation of LHON.

Vitamin B1 (Thiamine) Important in the mitochondrial metabolism of pyruvate via the pyruvate dehydrogenase enzyme complex for the production of energy.

Vitamin B2 (Riboflavin) Important in the mitochondrial electron transport chain as the co-factor for flavoproteins in the mitochondrial respiratory chain, especially in the functioning of Complex I and II of the electron transport chain. Folate (Vitamin B9) Important in the synthesis of mitochondrial DNA. Its deficiency may exacerbate the manifestation of LHON by enhancing oxidative stress. Antioxidants include Vitamins C and E, Coenzyme Q10, alpha-lipoic acid, and carotenoids, which play a vital role in the neutralization of ROS. In the presence of low antioxidant levels, the risk of oxidative stress. Thus, poor nutrition acts synergistically with environmental triggers to precipitate LHON expression. Preventive and Clinical Implications Nutritional counseling is an important preventive strategy for asymptomatic carriers: Ensure adequate B-complex vitamins and antioxidant-rich foods. Avoid extreme diets or malnutrition. Support mitochondrial function through balanced macronutrient intake. Supplementation with coenzyme Q10, idebenone, and antioxidants have been explored in clinical practice to reduce oxidative stress and preserve vision, especially in early diseases.

DIAGNOSTIC CRITERIA FOR LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

Leber's Hereditary Optic Neuropathy (LHON) is a mitochondrial genetic disorder characterized by acute or subacute, painless central vision loss. Early and accurate diagnosis is crucial for patient counseling, treatment initiation, and prevention of further visual deterioration.

CLINICAL EVALTION

a. History Taking Age of onset: Typically young adults (15–35 years), but can occur at any age Gender: Males are affected more frequently than females Vision loss: Sudden or subacute, painless, bilateral (sequential involvement common) Family history: Maternal inheritance pattern suggestive of mitochondrial disease Trigger factors: Smoking, alcohol intake, exposure to toxins, nutritional deficiency.

b. Visual Function Assessment Visual acuity: Rapid reduction, often to $\leq 6/60$ Color vision: Severe dyschromatopsia (red–green defect common) Contrast sensitivity: Markedly reduced Central scotoma: Detected early.

OPHTHALMIC EXAMINATION

a. Fundus Examination Findings vary with disease stage: Acute phase: Hyperemic optic disc

Peripapillary microangiopathy Telangiectatic vessels Absence of true disc edema Chronic phase: Optic disc pallor (temporal → diffuse) Retinal nerve fiber layer (RNFL) thinning.

b. Optical Coherence Tomography (OCT) Early RNFL thickening, especially temporally Progressive RNFL thinning in chronic stages Ganglion cell layer (GCL) loss is a sensitive early marker.

Visual Field Testing

Automated perimetry (Humphrey visual field) Dense central or cecocentral scotoma Useful for monitoring disease progression and response to therapy

*Electrophysiological Tests

a. Visual Evoked Potential (VEP) Reduced amplitude Delayed P100 latency Confirms optic nerve dysfunction.

b. Electroretinography (ERG) Typically normal. Helps exclude primary retinal disorders.

Neuroimaging

Magnetic Resonance Imaging (MRI) MRI brain and orbit usually normal Helps rule out: Optic neuritis Multiple sclerosis Compressive or inflammatory optic neuropathies.

Genetic Testing (Confirmatory Diagnosis)

a. Mitochondrial DNA Analysis

Gold standard for LHON diagnosis

Common pathogenic mutations:

m.11778G>A (ND4) – most common, poor prognosis

m.14484T>C (ND6) – better visual recovery

m.3460G>A (ND1)

b. Heteroplasmy Assessment

Determines mutation load Influences disease expression and severity.

Biochemical and Laboratory Investigations

Serum vitamin B12, folate, Lactate levels (occasionally elevated). Exclusion of: Toxic optic neuropathy Nutritional optic neuropathy.

Differential Diagnosis

Conditions to be ruled out: Optic neuritis, Dominant optic atrophy, Toxic/nutritional optic

neuropathy, Compressive optic neuropathy, Ischemic optic neuropathy.

Multidisciplinary Evaluation

Neurologist: For associated neurological features (LHON-plus). Genetic counseling: Essential psychological support for family screening: Due to sudden vision loss.

INNOVATIVE IMAGING TECHNIQUES FOR IDENTIFICATION OF LEBER 'S HEREDITARY OPTIC NERUOPATHY

New techniques in imaging, genetics and functional optics have enhanced the ability to diagnose, predict outcomes and evaluate ongoing status of LHON. Around the world, multiple approaches are being utilized in conjunction to evaluate LHON.

Advanced Optical Coherence Tomography (OCT)

a. Spectral Domain OCT (SD-OCT) Provides high resolution assessment of RNFL and GC-IPL. Typically, SD-OCT will show early thickening of temporal RNFL followed by thinning. Size and loss of GC-IPL are considered to be early indicators of disease progression prior to loss of vision.

b. Swept Source Optical Coherence Tomography (SS-OCT)

Allows better penetration into deeper tissues to visualize the optic nerve head and choroidal thickness and is being utilized in international tertiary care centers for long term evaluation of LHON.

Optical Coherence Tomography (OCT) Angiography

Non-invasive imaging techniques are used to evaluate the microvascular anatomy of the retina and optic nerve. Detect anomalies such as peripapillary capillary drops, and decreased vessel density in both superficial and deep capillary plexus, to help distinguish LHON from optic neuritis. OCT Angiography is an important diagnostic and prognostic test.

Adaptive Optics Imaging

Provides ultra-high-resolution imaging at the cellular level. Allows for direct visualization of retinal ganglion cell degeneration and the integrity of cone photoreceptors. Used primarily in research and advanced clinical trials, AO Imaging is capable of identifying subclinical disease in individuals who are carriers.

ADVANCED DIAGNOSTIC MODALITIES USED INTERNATIONALLY IN LEBER'S HEREDITARY OPTIC NEUROPATHY(LHON)

Recent advances in ocular imaging, molecular genetics, and functional neuro-ophthalmology have significantly improved the early diagnosis, prognostication, and disease monitoring of Leber's Hereditary Optic Neuropathy (LHON). Internationally, a multimodal diagnostic strategy is now adopted.

Advanced Optical Coherence Tomography (OCT) Techniques

a. Spectral-Domain OCT (SD-OCT) High-resolution assessment of: Retinal Nerve Fiber Layer (RNFL) Ganglion Cell–Inner Plexiform Layer (GC-IPL) Early temporal RNFL thickening followed by progressive thinning GC-IPL loss is considered an early biomarker before visual loss.

b. Swept-Source OCT (SS-OCT) Deeper tissue penetration better visualization of: Optic nerve head Choroidal thickness Used in international tertiary centres for longitudinal monitoring.

OCT Angiography (OCTA)

Non-invasive assessment of retinal and optic nerve microvasculature Detects: Peripapillary capillary dropout Reduced vessel density in superficial and deep plexus Helps differentiate LHON from optic neuritis Considered a key advanced diagnostic and prognostic tool.

Adaptive Optics Imaging

Ultra-high-resolution imaging at cellular level Direct visualization of: Retinal ganglion cell degeneration Cone photoreceptor integrity Used mainly in research and advanced clinical trials Allows detection of subclinical disease in asymptomatic carriers.

Advanced Visual Field and Functional Testing

a. Microperimetry: Maps retinal sensitivity corresponding to macular structure. Detects early central scotoma. Useful for correlating structure–function relationship.

b. Contrast Sensitivity Testing: More sensitive than Snellen acuity. Early functional impairment marker.

Advanced Electrophysiological Diagnostics

a. Pattern Electroretinogram (PERG) Sensitive indicator of retinal ganglion cell dysfunction Abnormal PERG may appear before OCT changes.

b. Multifocal Visual Evoked Potential (mfVEP) provides localized optic nerve function mapping. Useful in early or atypical LHON cases.

High-Resolution Neuroimaging

- a. Diffusion Tensor Imaging (DTI-MRI) Evaluates optic nerve microstructural integrity. Shows reduced fractional anisotropy in LHON. Detects early axonal damage before conventional MRI changes.
- b. Functional MRI (fMRI) Assesses visual cortex activation. Demonstrates cortical reorganization in chronic LHON. Primarily used in research and international centres.

Advanced Genetic Diagnostics

- a. Next-Generation Sequencing (NGS), Comprehensive mitochondrial genome sequencing
Identifies: Rare LHON mutations, Secondary mitochondrial variants. Widely used in Europe, USA, and Japan.
- b. Whole Exome / Genome Sequencing Detects nuclear modifier genes. Useful in LHON-plus syndromes
- c. Digital PCR Precise quantification of heteroplasmy levels. Important for prognosis and carrier screening

Metabolomic and Biomarker Studies (Emerging)

Measurement of: Mitochondrial respiratory chain metabolites Oxidative stress markers. Plasma and CSF biomarkers under investigation Used mainly in international research trials.

Artificial Intelligence (AI)–Based Diagnostics

AI-assisted OCT and fundus image analysis. Early detection of subtle RNFL and GCL changes predicts disease conversion in asymptomatic carriers. Currently used in advanced academic centres.

Carrier Screening and Predictive Diagnostics

Asymptomatic maternal relatives screened using: CT + OCTA. Genetic testing helps in early lifestyle modification and counselling.

TREATMENT AND MANAGEMENT STRATEGIES IN LEBER'S OPTIC NEUROPATHY (LHON)

Leber's Hereditary Optic Neuropathy (LHON) is a mitochondrial optic neuropathy with limited spontaneous recovery. Management focuses on early intervention, mitochondrial support, gene-based therapies, and long-term visual rehabilitation, using a multidisciplinary approach.

Acute-Phase Management

a. Early Diagnosis and Prompt Intervention Early initiation of therapy (within weeks of symptom onset) improves outcomes Bilateral monitoring due to high risk of sequential eye involvement.

Pharmacological Therapy

a. Idebenone (Approved Therapy) A short-chain benzoquinone, synthetic analogy of coenzyme Q10 Mechanism: Bypasses mitochondrial complex I dysfunction Improves ATP production Reduces oxidative stress Dose (international practice): 900 mg/day orally (300 mg three times daily) Most effective when started earliest response seen in m.14484T>C mutation Approved in Europe (EMA); used off-label in many countries.

b. Coenzyme Q10 and Analogs: Support mitochondrial electron transport. Used as adjunctive therapy Evidence is weaker than that of idebenone.

Gene Therapy (Advanced & Emerging Treatment)

a. Allotropic Gene Therapy (AAV-ND4) Adeno-associated viral (AAV) vector delivering the ND4 gene. Intravitreal injection Trials showed: Visual improvement in both treated and untreated eyes (bilateral effect). Approved in some regions and under extended access programs. It represents a disease-modifying therapy.

Antioxidant and Mitochondrial Support Therapy

Alpha-lipoic acid Riboflavin (Vitamin B2) Thiamine (Vitamin B1) L-carnitine
Vitamin C and Purpose: Reduce oxidative stress, support mitochondrial metabolism.

Lifestyle Modification and Risk Factor Control

Strongly recommended internationally: Complete smoking cessation Avoid alcohol consumption Avoid exposure to mitochondrial toxins (e.g., certain antibiotics, solvents), and stress reduction. These measures significantly reduce disease penetrance and progression.

Nutritional Management

Correct deficiencies.

Vitamin B12 folate vitamin D

Balanced diet rich in.

Antioxidants Omega fatty acids malnutrition worsens mitochondrial dysfunction.

Visual rehabilitation and supportive care

- a. Low vision aids Magnifiers Electronic visual aids Screen readers
- b. Occupational therapy adaptive training for daily activities mobility and orientation training
- c. Psychological support counselling for anxiety and depression Quality-of-life improvement

Genetic counselling and family screening maternal inheritance explained to patient and families

Screening of asymptomatic carriers counselling regarding reproductive options lifestyle risk factors prenatal and preimplantation genetic diagnosis (PGD) discussed internationally.

Management of LHON -plus syndromes for patients with associated neurological features.

Multidisciplinary care (neurology, cardiology) movement disorders cardiac conduction defects peripheral neuropathy.

Experimental and future therapies

A Mitochondrial biogenesis activators agents targeting PCG-1 α pathway c. CRISPR-Based mitochondrial editing future personalized potential.

EUROPE: REGULATORY APPROVAL AND CLINICAL USE REGULATORY STATUS

Approved indication: Idebenone (as Raxone® with 150mg tablets) is officially authorised by the European medicines agency (EMA) for the treatment of visual impairment in adolescent and adult patient with LHON. European medicines agency (EMA) it holds the status of an orphan medicine due to the rarity and severity of LHON, which allows certain incentive but requires ongoing data collection. European Medicines Agency (EMA) The EMA authorisation was granted under exceptional circumstances given limited but clinically meaningful evidence on effectiveness and safety. European medicines agency (EMA) Clinical Evidence and Guidelines. The RHODOS phaseIII study (traditional RCT) and later LEROS and other real-world observational series have shown a trend toward visual improvement or stabilization with idebenone compared to natural history, particularly when treatment is started early in the disease course (With 1-5years from onset). Nature+ A recent systematic review/meta – analysis (2025) reports a clinically relevant improvement in visual acuity with idebenone. Some national bodies in Europe (e.g., NICE in the UK) include idanone in therapeutic guidance for LHON. NCBI clinical practice trends typically dosed at

900mg/day (300mg tads) with food. European medicines agency (EMA) Efficiency is greatest in the acute /subacute phase, with benefits becoming less clear in very chronic (>5years) cases. PMC Monitoring includes visual acuity and safety labs, and treatment continuation is generally considered for ~12-24+ months based on clinical response. European medicines agency (EMA) Established regulatory approval with a formal marketing authorisation for LHON. Evidence support use mainly in early disease; long-term benefits and best patient subsets remain areas of ongoing investigation.

India: current status and use of regulatory and market reality

Unlike Europe, there is no known disease-specific regulatory approval in India for idebenone (or Raxone®) specifically for LHON under India's drug regulatory system (CDSCO). There is no official Indian regulatory listing or marketing authorisation (similar to EMA) publicly documented as of early 2026 (no CDSCO label for idebenone in LHON). Generic idebenone tablets (e.g., 45mg and 90mg formulations) are marketed in India, typically as antioxidant therapy or marketed in India, typically as antioxidant therapy or for other uses (such as Friedreich's ataxia or "vision impairment" in practice), but these indications are broadly stated on commercial labelling rather than based on an approved LHON indication. In clinical practice, off-label for LHON by neuro-ophthalmologists or genetic specialists when locally available permits, but this is not an approved indication per se under Indian regulatory frameworks. Availability and prescribing available through local pharmacies as generic idebenone tablets; prescription required (schedule H). A physician may base its use on international clinical literature and case series; formal Indian guidelines specifically endorsing idebenone for LHON are lacking. Challenges and limitation in India regulatory approval gap: No formal authorised label for LHON, so use is dependent on physician discretion/off-label use. Cost and access: Without formal reimbursement pathways, cost can be a barrier for many patients. Evidence translation: most trial evidence and guidelines are European- centric; Indian clinical experience may be limited.

PROGNOSIS AND VISUAL RECOVERY IN LEBER'S HEREDITARY OPTIC NEUROPATHY

Typical Clinical Course LHON usually presents as subacute, painless bilateral central vision loss, progressing over a few weeks to profound visual impairment. For most patients, the visual loss is severe and permanent, leading to optic atrophy and dense central scotomas. Spontaneous visual recovery occurs only in a minority of cases and typically manifests within

months to a few years after onset.

Factors Influencing Prognosis

Mitochondrial DNA Genotype

The type of mtDNA mutation is one of the strongest predictors of visual outcome: m.11778G>A mutation – the most common variant worldwide, generally has a poor prognosis. Spontaneous meaningful recovery (e.g., ≥ 3 lines on an ETDRS chart) occurs in a small percentage of patients (around 4–11%), depending on definitions and cohorts. m.14484T>C mutation – is associated with the best spontaneous recovery rates, reported in many studies as ~37–65% of affected individuals experiencing some degree of visual improvement. m.3460G>A mutation – shows recovery rates intermediate or similar to the 11778 variant, with less consistent data. These patterns are reflected in both natural history and observational studies, with the m.14484T>C variant often linked to better long-term visual outcomes.

Age at Onset

Younger age at onset, particularly <20 years, is strongly correlated with a better visual prognosis, including higher rates of recovery. Patients presenting before age 15 (especially <12 years) tend to have more favourable outcomes than older individuals.

Severity at Nadir

The minimum visual acuity reached early in the disease also predicts recovery potential. Eyes that do not drop to extremely low acuity levels (e.g., ≥ 0.04 decimal acuity) in the first year are significantly more likely to regain useful vision compared with eyes with very severe nadir vision. Patterns of Visual Recovery Spontaneous Recovery Spontaneous recovery refers to improvement without specific therapeutic interventions and is reported to occur over a range of months to up to 10 years after onset. Recovery may manifest as a gradual improvement in central visual acuity or occasionally as small “islands” of central vision emerging within a dense scotoma. Some case series have documented recovery to near-normal levels (e.g., >20/40 in at least one eye) even after years of severe impairment, although this is uncommon. Mutation-Specific Differences For the 11778 mutation, spontaneous recovery is rare ($\approx 4\%$ historically) but has been variably reported up to ~11% in certain cohorts when broader recovery criteria are applied. For the 14484 mutation, recovery rates are substantially higher: up to ~37–65% in many studies, with younger patients particularly more likely to improve. Timing and Magnitude Most visual improvements occur

within the first 1–2 years after onset, although later recovery (up to a decade) has been documented in rare cases. NCBI The degree of recovery varies widely — from mild improvements insufficient to change functional status, to meaningful gains in visual acuity, including regaining the ability to read or navigate independently. Clinical Implications Prognostic assessment in LHON should include genetic testing to identify the specific mutation, as this strongly informs the likelihood of recovery and counselling at symptom onset and severity of visual loss at nadir help stratify patients into higher or lower likelihood categories for spontaneous or treatment-related improvement. Supportive care (vision rehabilitation, low-vision aids) is critical for patients with permanent vision loss. Even moderate spontaneous improvement can significantly affect quality of life and functional independence. Emerging modifiers of prognosis Novel therapies such as idebenone and gene therapy are being investigated and, in some studies, are associated with improved visual outcomes beyond natural history, although response varies widely and long-term data are still emerging.

MUTATION SPECTRUM IN INDIA PATIENTS

Many Indian LHON studies show that the three classic primary mtDNA mutations — m.11778G>A, m.3460G>A, and m.14484T>C — are present but at variable frequencies compared to global reports. Unlike many Western populations where m.11778G>A is dominant and often associated with specific mtDNA haplogroups like haplogroup J, Indian cases show m.11778G>A is still the most common but with diverse mtDNA backgrounds (multiple haplogroups). There is no strong association between a specific haplogroup and disease expression in Indian subjects — unlike the preference for haplogroup J seen elsewhere.

Variation in Mutation Detection Rates

Different Indian cohorts report different rates of detection of primary mutations: One North Indian study found ~27.5% with the m.11778A mutation among LHON patients. Larger screening from an Indian tertiary centre reported ~29–43.6% of patients having one of the three primary mutations, with m.11778G>A again being most frequent. Some Indian studies also find secondary mtDNA variants and novel mutations that standard screening may miss — indicating a broader genetic spectrum.

Clinical and Genetic Heterogeneity

Many Indian patients with typical clinical LHON signs do not carry the classic primary

mutations at all — a pattern less common in Western cohorts. This suggests: HON in Indian patients may have distinct genetic architecture Standard mtDNA mutation panels detect fewer variants here compared to other global populations.

Phenotype Differences and Clinical Expression

Studies from South India report similar clinical severity among mutation groups (like m.11778A vs m.14484C), with some trends such as greater nerve Fiber thinning in certain mutations, but overall differences are subtle and not always statistically significant. Lippincott Journals Male predominance, early adulthood onset, and variable penetrance seen in Indian studies mirror global patterns.

PSYCHOSOCIAL IMPACT OF LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

Leber's Hereditary Optic Neuropathy (LHON) is a rare inherited eye disorder that mainly affects young people, especially males. It causes sudden or gradual loss of central vision in one or both eyes. Apart from vision loss, LHON has a strong psychosocial impact, which means it affects a person's mental health, emotions, behaviour, family life, education, work, and social relationships. Understanding these impacts is very important for providing complete care to LHON patients.

Emotional and Psychological Impact

Vision loss in LHON often occurs suddenly, which can be very shocking. Patients may experience: Shock and denial after diagnosis Fear and anxiety about future blindness Depression and sadness due to loss of independence Anger and frustration when unable to perform daily activities young patients may feel helpless and worried about their future. Long-term visual impairment can increase the risk of clinical depression and chronic stress, especially if emotional support is poor.

Impact on Self-Confidence and Identity

LHON commonly affects adolescents and young adults, a stage when personal identity is still developing. Vision loss can lead to: Low self-esteem Feeling of being "different" from others Loss of confidence in public places Embarrassment while using visual aids like white canes or magnifiers Some patients avoid social situations due to fear of stigma or pity from others.

Educational Challenges

For students, LHON creates major difficulties in education: Difficulty reading textbooks and blackboards Slower learning due to visual limitations Dependence on others for notes and study materials Reduced academic performance Without proper support such as large-print books, screen readers, audio materials, and special education services, students may drop out of school or lose interest in Studie

Occupational and Financial Impact

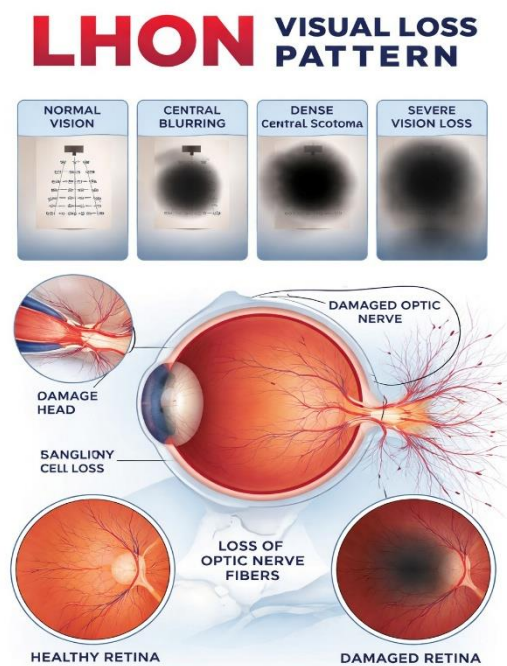
Vision loss affects job

opportunities and career planning: Difficulty continuing visually demanding jobs Limited career choices Workplace discrimination or misunderstanding Unemployment or underemployment Loss of income and high medical expenses can lead to financial stress, affecting both patients and their families Social Relationships and Isolation LHON can negatively affect social life: Reduced participation in social activities Difficulty recognizing faces and social cues Dependence on family members or friends Feeling like a burden to others Many patients experience social isolation, which can further worsen mental health problems. Family and Caregiver Burden Since LHON is a genetic disorder, it impacts the entire family: Parents may feel guilt for passing the mutation Family members may fear developing the disease Increased caregiving responsibilities Emotional and financial strain on.

IMPACT OF LEBER'S HEREDITARY OPTIC NEUROPATHY ON EDUCATION AND EMPLOYMENT

Leber's Hereditary Optic Neuropathy (LHON) is a rare, maternally inherited mitochondrial disorder that leads to rapid, painless central vision loss, typically in young adulthood — most often between the ages of 15 and 35. It disproportionately affects males and leads to significant visual impairment that becomes permanent within about a year of onset. SpringerLink +1Early Life and Education Challenges Vision loss from LHON often occurs during crucial educational years, such as late high school or early university. Sudden deterioration in central vision makes tasks like reading textbooks, writing exams, and using computers extremely difficult without appropriate accommodations. Central vision is critical for reading, recognizing faces, and detailed work foundational skills in most learning environments. SpringerLink Many students with LHON face interruptions in their schooling: Study discontinuation and delay: Research shows a notable portion of people with LHON discontinue their studies after symptom onset, with central vision loss interfering with reading and completing assignments. PMC Adaptation needs: Students must often shift to large-print materials, screen-reading software, audio textbooks, Braille (where available), or tactile learning aids to continue their education effectively. These require both institutional support and access to resources, which may not always be available or affordable. Without early diagnosis and support, many LHON-affected students experience frustration and a sense of academic setback, especially in visually intensive subjects. This can lead to missed opportunities in competitive academic fields, reduced academic achievement, and long-term changes in career pathways. Transition to Employment: New Realities and Barriers Vision

loss during young adulthood coincides with the time when most individuals enter the workforce. LHON can therefore significantly impact employment prospects, career choices, and long-term job stability. Reduced Work Participation and Productivity Even among those who remain employed, LHON often results in: Reduced productivity (presenteeism): Individuals working with LHON may experience up to nearly 50 % reduction in work capacity due to vision-related challenges. In one study, average presenteeism — being present but less productive — accounted for a major portion of lost workplace productivity. SpringerLink Work impairment: Research has shown an overall work impairment (including decreased performance and increased difficulty completing tasks) that can have economic consequences for both employees and employers. Unemployment and Disability Support Some individuals with LHON may transition out of the workforce entirely, especially in jobs that require sharp central vision, such as driving, detailed manual labour, or jobs heavily reliant on visual input. In documented cases: A significant percentage (over 20 %) of LHON patients were unemployed or received disability pensions. SpringerLink This strain reflects both the direct disability impact of vision loss and the indirect socio-economic burden, including the potential need for assistive technologies, workplace accommodations, and retraining for new roles suited to individuals with visual impairment. Psychosocial and Long-Term Career Adjustments Vision loss not only affects practical abilities but also influences psychological well-being, confidence, and career aspirations: Mental health challenges: Many individuals report frustration, loss of independence, and anxiety about their academic and professional futures, especially when onset is sudden. Career reorientation: LHON often demands that individuals rethink their career paths. Some may shift to fields that can be adapted to visual impairment, such as technology (with accessibility tools), counselling, administration, writing, or advocacy. Adaptation & resilience: Despite challenges, many individuals with LHON build successful careers with the right support, using assistive technologies and workplace accommodations to perform tasks that once seemed impossible without sight.



Support Systems and Solutions Addressing the educational and employment impact of LHON involves a multifaceted support framework: Educational Accommodations Provision of accessible materials (large print, audio, Braille) Extended exam times and assistive tech support Training for educators to understand LHON and visual impairment Workplace Adaptations Screen-reader software, voice recognition, and adaptive hardware Flexible roles matched to strengths rather than visual tasks Government or employer-supported disability accommodations Policy and Advocacy. Public awareness and inclusive policies are key to ensuring persons living with LHON are not sidelined. Disability laws, vocational training programs, and targeted funding for assistive technology help level the educational and employment playing field.

SOCIAL SUPPORT SYSTEMS IN INDIA VS DEVELOPED COUNTRIES

Social support systems play a crucial role in determining health outcomes, quality of life, educational continuity, and employment opportunities for individuals living with chronic illnesses and disabilities, including rare genetic disorders such as Leber's Hereditary Optic Neuropathy (LHON). A comparison between India and developed countries highlights substantial differences in structure, accessibility, funding, and societal integration of support mechanisms.

Concept and Scope of Social Support Systems

Social support systems broadly include healthcare services, financial assistance, disability benefits, educational accommodations, employment protection, rehabilitation services, psychological counselling, and community-based support. In developed countries, these systems are typically institutionalized, rights-based, and backed by strong policy frameworks. In contrast, India's social support system is more fragmented, with a combination of government schemes, non-governmental organizations (NGOs), and family-based care forming the backbone of support.

Healthcare Access and Financial Protection

In developed countries, universal or near-universal health coverage ensures early diagnosis, specialist consultation, genetic testing, and long-term management for rare diseases. Health insurance schemes often cover advanced diagnostics, assistive devices, rehabilitation, and in some cases, orphan drugs. Patients benefit from structured referral systems and multidisciplinary care teams. In India, although public healthcare services exist, access to specialized care for rare diseases remains limited. Out-of-pocket expenditure is high, and advanced genetic testing or long-term therapies are often unaffordable. Government initiatives such as Ayushman Bharat have improved coverage for economically vulnerable populations, but rare diseases and chronic disabilities still receive limited financial protection. As a result, families often bear the primary economic burden of care.

Disability Benefits and Social Security

Developed countries provide comprehensive disability benefits through social security systems. These include monthly disability pensions, income replacement, tax benefits, subsidized housing, transportation allowances, and assistive technologies. Eligibility criteria are clearly defined, and benefits are legally enforceable. In India, disability-related benefits are available under schemes such as the Rights of Persons with Disabilities (RPwD) Act, 2016. These include disability certificates, limited pensions, travel concessions, and reservations in education and employment. However, benefit amounts are relatively low, implementation varies across states, and administrative barriers often delay or restrict access. Awareness among patients and families is also limited.

Educational Support and Inclusion

Educational systems in developed countries emphasize inclusive education. Students with visual impairment or other disabilities receive individualized education plans (IEPs), assistive

technologies (screen readers, braille devices), trained special educators, and examination accommodations. Early intervention programs help minimize educational disruption. In India, inclusive education policies exist, but implementation is inconsistent. Special schools and resource centres are concentrated in.

MENTAL HEALTH CONSIDERATION IN LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

Leber's Hereditary Optic Neuropathy (LHON) is not only a mitochondrial optic neuropathy leading to profound visual impairment but also a condition with significant mental health implications. The sudden onset of bilateral central vision loss, often affecting adolescents and young adults during critical educational and occupational phases, places individuals at heightened risk for psychological distress. Psychological Impact of Sudden Vision Loss. The acute and often irreversible nature of vision loss in LHON can trigger strong emotional reactions, including shock, fear, anger, and grief. Many patients experience an adjustment disorder in the early stages, characterized by emotional instability and difficulty adapting to functional limitations. The unpredictability of disease progression and uncertain visual prognosis further exacerbate anxiety. Depression and Anxiety Disorders Depressive symptoms are commonly reported among individuals with LHON, particularly in those with severe and permanent visual impairment. Loss of independence reduced mobility, and inability to pursue previous academic or career goals contribute to feelings of hopelessness and low self-esteem. Anxiety disorders may arise from concerns about social participation, future employment, and financial stability. Fear of disease transmission to offspring, due to maternal inheritance, may also contribute to chronic stress. Social Isolation and Stigma Visual disability can lead to social withdrawal, especially in settings where awareness and accessibility are limited. In developing countries, social stigma associated with disability may intensify feelings of shame and marginalization. Reduced participation in social, recreational, and cultural activities negatively affects overall quality of life and emotional well-being. Cognitive and Neuropsychiatric Associations Emerging evidence suggests that mitochondrial dysfunction in LHON may have broader neurological and neuropsychiatric implications. Some individuals, particularly those with LHON-plus phenotypes, exhibit increased vulnerability to mood disorders, cognitive fatigue, and, rarely, psychotic symptoms. These manifestations may reflect systemic mitochondrial impairment affecting the central nervous system. Impact on Family and Caregivers LHON imposes a psychological burden not only on patients but also on family members and caregivers. Parents and spouses may experience

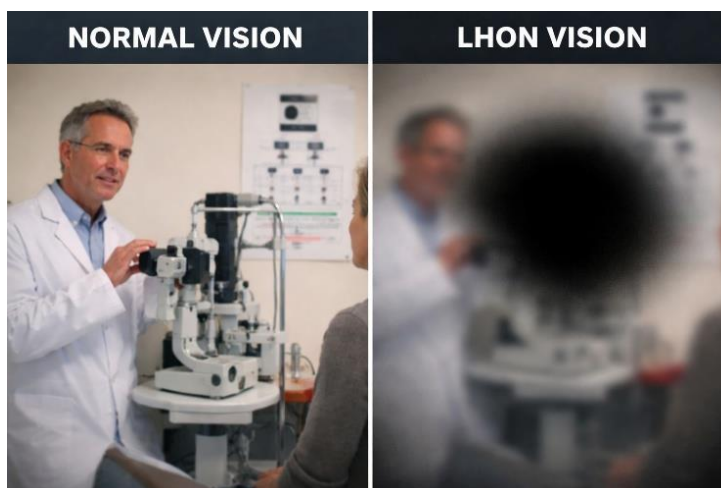
guilt, anxiety, and emotional exhaustion while adapting to caregiving roles. Family dynamics can be strained, emphasizing the need for psychosocial support at the family level. Importance of Mental Health Screening and Support Routine mental health screening should be integrated into the clinical management of LHON. Early identification of depression, anxiety, and adjustment difficulties allows timely intervention. Psychological counselling, cognitive-behavioural therapy, peer support groups, and vision rehabilitation programs play a crucial role in improving coping strategies and resilience. Holistic and Multidisciplinary Management optimal LHON care requires a multidisciplinary approach that addresses both visual and psychological outcomes. Collaboration among ophthalmologists, neurologists, psychiatrists, psychologists, and rehabilitation specialists can enhance quality of life. Patient education, genetic counselling, and vocational guidance further support mental well-being and long-term adaptation.

GENETIC COUNSELING AND AWARENESS IN LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

Leber's Hereditary Optic Neuropathy (LHON) is a maternally inherited mitochondrial disorder, most commonly caused by point mutations in mitochondrial DNA (mtDNA). Given its unique inheritance pattern, incomplete penetrance, and variable clinical expression, genetic counselling and disease awareness are essential components of comprehensive LHON management. Role of Genetic Counselling in LHON Genetic counselling plays a critical role in helping patients and families understand the nature of LHON, its inheritance, and its potential impact on future generations. Since mtDNA is transmitted exclusively through the maternal line, female carriers have the potential to pass pathogenic mutations to all offspring, whereas affected males do not transmit the disease. Counselling helps clarify this pattern and correct common misconceptions about genetic risk. Risk Assessment and Family Screening Genetic counselling facilitates accurate risk assessment for asymptomatic carriers and family members. Not all individuals carrying LHON-associated mutations develop visual loss, highlighting the importance of explaining incomplete penetrance and sex bias, with males being more frequently affected. Family-based genetic screening enables early identification of mutation carriers, allowing for monitoring, lifestyle modifications, and early intervention when visual symptoms appear. Reproductive Counselling and Family Planning. Reproductive counselling is particularly important for women who carry LHON mutations. Counsellors provide information on the probability of disease expression in offspring and discuss available reproductive options. These may include prenatal diagnosis, preimplantation

genetic testing, and emerging mitochondrial replacement therapies in countries where they are ethically and legally approved. Such discussions empower families to make informed reproductive decisions. Lifestyle and Environmental Risk Awareness programs emphasize the role of environmental and lifestyle factors—such as smoking, excessive alcohol consumption, and exposure to mitochondrial toxins—that may trigger disease expression in genetically susceptible individuals. Educating carriers about modifiable risk factors can reduce the likelihood of phenotypic conversion and improve long-term outcomes. Psychosocial Support and Ethical Considerations Genetic counselling in LHON also addresses psychosocial challenges, including anxiety, guilt, and fear related to genetic transmission. Disclosure of carrier status may affect family relationships and marriage prospects in certain cultural contexts. Ethical issues such as genetic testing of minors, confidentiality, and informed consent must be handled sensitively by trained professionals. Importance of Public and Professional Awareness. Limited awareness of LHON among healthcare providers and the general population often leads to delayed diagnosis and mismanagement. Increasing awareness through medical education, public health initiatives, and patient advocacy groups can promote early referral for genetic testing and counselling. In resource-limited settings, strengthening genetic literacy among clinicians is particularly important. Integration into Multidisciplinary Care Genetic counselling should be integrated into a multidisciplinary LHON care model involving ophthalmologists, neurologists, geneticists, and mental health professionals. Continuous education and follow-up counselling help patients adapt to evolving clinical and familial circumstances, ultimately improving quality of life.

AWARENESS OF LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON) IN INDIA



Leber's Hereditary Optic Neuropathy (LHON) remains a poorly recognized condition within India's public health landscape, reflecting broader challenges in awareness of rare genetic diseases. Unlike more common ocular diseases, LHON is seldom featured in primary care training or public health campaigns, contributing to delayed diagnosis and mismanagement.

Clinical Recognition and Diagnostic Awareness. LHON diagnosis in India is largely initiated at tertiary neuro-ophthalmology centres and academic hospitals, where clinicians with specialized training recognize its characteristic bilateral painless central vision loss in young adults. Studies from tertiary centres report cohorts of clinically and genetically assessed LHON cases, indicating that most diagnoses occur where neuro-ophthalmologists and genetic testing are available. Nevertheless, there is no robust population-level data on referral patterns, and many patients remain undiagnosed or misclassified under generic optic atrophy due to limited awareness at the primary care level.

Genetic Testing and Counselling Awareness While genetic testing for LHON has been reported in multiple Indian cohorts, the proportion of patients with confirmed primary mutations (such as m.11778G>A) is variable, with less than a third to under half of clinically suspected patients testing positive for the common mutations. This variability reflects both genetic heterogeneity and the inconsistent uptake of comprehensive molecular diagnostics. Genetic counselling, a cornerstone of LHON management, is practiced primarily in specialized centers but remains inaccessible or underutilized in many regions, especially where genetic services are limited.

Public and Healthcare Professional Awareness in India, LHON sits within the broader category of rare genetic diseases, which historically have had low visibility in public health policy and medical training. National initiatives such as the National Policy for Rare Diseases (NPRD) 2021 acknowledge the need for awareness and early detection of rare conditions through clinician education and public outreach, but implementation gaps persist. Rare disease awareness campaigns (e.g., Rare Disease Day) aim to highlight conditions like LHON, but specific disease-focused awareness remains limited.

Barriers to Awareness and Early Diagnosis Several systemic challenges constrain LHON awareness in India: Limited inclusion in medical curriculum and continuing medical education, leading to under-recognition by general ophthalmologists and primary care physicians. Scarcity of genetic counselling infrastructure outside major cities, limiting informed discussions about inheritance and family risk. Public health focus on more prevalent diseases, which diverts attention and resources from rare conditions such as LHON. Socioeconomic disparities in access to specialized care, which can delay referral and accurate diagnosis.

Positive Trends and Future Directions Despite these barriers, awareness is gradually increasing within

specialist circles. Neuro-ophthalmology clinics in tertiary centers report growing numbers of referrals and diagnoses, suggesting improving clinical recognition. Additionally, national rare disease initiatives and expanding genomics research networks (e.g., Guardian) are enhancing diagnostic capacity and may indirectly improve disease-specific awareness over time.

RESEARCH TRENDS AND GAPS IN LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

India has increasingly contributed to the clinical, genetic, and epidemiological understanding of Leber's Hereditary Optic Neuropathy (LHON), particularly through hospital-based studies and genomic research that reflect the diverse genetic backgrounds of Indian populations. Early Clinical and Molecular Characterization Initial molecular documentation of LHON in India dates back to case reports and small family studies, where classic mitochondrial mutations (e.g., G3460A and G11778A) were identified in affected families using PCR-based methods. These foundational studies helped establish the presence of LHON in Indian cohorts and underscored the importance of genetic testing in suspected optic atrophy cases. Prevalence and Mutation Frequency Studies. Large hospital-based studies have significantly expanded epidemiological insights. At southern and northern Indian tertiary eye care centres, researchers have screened clinically suspected LHON patients for the three common mitochondrial mutations (m.3460G>A, m.11778G>A, m.14484T>C). These studies found that roughly 25–30 % of clinically suspected Indian patients carry one of the primary mutations, with m.11778G>A being the most frequent. A prospective five-year genetic screening at Aravind Eye Hospital (Madurai) revealed an estimated clinic prevalence of LHON among referred optic neuropathy cases and confirmed the presence of primary mitochondrial mutations in a substantial proportion of patients. Whole Mitochondrial Genome and Haplogroup Analyses. Beyond screening for primary mutations, comprehensive whole mitochondrial genome analyses in South Indian patients have identified numerous variants and suggested an association with specific haplogroups (e.g., haplogroup M) that may influence disease expression in Indian populations.

Large cohort studies examining 64 families with the m.11778G>A mutation demonstrated that this mutation occurs against a wide variety of mitochondrial haplogroup backgrounds in India and highlighted variable penetrance patterns, differing from patterns described in Western cohorts. Emerging Genomic and Nuclear Modifier Research. Recent Indian research has moved into exploring Mito-nuclear genetic factors in LHON. Comprehensive genomic

profiling in a cohort of probands revealed that many individuals lack classic primary mtDNA mutations, and whole exome sequencing identified pathogenic variants in several nuclear genes. This work suggests that nuclear-encoded factors may contribute to LHON phenotypes, especially in cases without primary mtDNA mutations. Case Reports and Clinical Insight In addition to genetic studies, Indian clinicians have published case reports that highlight diagnostic challenges, emphasize the role of genetic testing in differential diagnosis, and call attention to the need for improved awareness among general ophthalmologists and neurologists. Ongoing and Emerging Work Recent case series and descriptive studies from Indian neurology and ophthalmology centres have begun to report on therapeutic experiences (e.g., idebenone treatment) and clinical outcomes in genetically confirmed LHON patients, indicating a shift toward translational and interventional research within the Indian clinical setting. Indian research on LHON has evolved from initial case descriptions and mutation detection to large genetic screening cohorts, whole-genome analyses, and now Mito-nuclear interaction studies. These contributions significantly enhance understanding of the genetic heterogeneity, phenotypic variability, and population-specific aspects of LHON in India. However, further multicentre and population-based studies are needed to refine prevalence estimates, understand modifier factors, and evaluate potential interventions.

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Delayed and Missed Diagnosis

One of the most significant challenges in developing countries is delayed or incorrect diagnosis. LHON often presents as painless, subacute vision loss in young males, a

demographic commonly affected by optic neuritis, nutritional optic neuropathy, or toxic optic neuropathies in LMICs. Due to overlapping clinical features and limited access to advanced diagnostic tools, LHON is frequently misdiagnosed, leading to inappropriate treatment and delayed counselling. Limited availability of genetic testing facilities is a major barrier. Mitochondrial DNA analysis for common mutations (m.11778G>A, m.3460G>A, m.14484T>C) is largely confined to tertiary centres, often located in urban regions. As a result, many patients remain undiagnosed or are diagnosed late, beyond the therapeutic window for potential interventions.

Limited Access to Advanced Diagnostic Technologies

Advanced diagnostic modalities such as optical coherence tomography (OCT), visual evoked potentials (VEP), fundus autofluorescence, and mitochondrial genetic testing are not uniformly available in developing countries. Even when available, the cost associated with these investigations places them beyond the reach of many patients. In rural and semi-urban settings, ophthalmology services often lack subspecialty neuro-ophthalmology expertise, resulting in reliance on clinical judgment alone. This further increases the risk of under-recognition of LHON and delays in referral to specialized centers.

Economic Constraints and Treatment Affordability

Economic burden represents a critical challenge. Approved or investigational therapies for LHON, such as idebenone or gene therapy, are expensive and largely inaccessible in developing countries. Idebenone is not universally approved or reimbursed in many LMICs, including India, and long-term treatment costs are prohibitive for most patients. Gene therapy, although promising, remains largely unavailable due to high costs, lack of regulatory approval, and absence of specialized infrastructure required for administration and follow-up. Consequently, patients in developing countries are often limited to supportive care rather than disease-modifying interventions.

Low Awareness Among Healthcare Professionals and the Public

Awareness of LHON among primary care physicians, general ophthalmologists, and neurologists is limited in developing countries. This contributes to delayed referrals, unnecessary investigations, and inappropriate treatments such as prolonged corticosteroid use. Public awareness is also extremely low. Visual loss in young individuals is often attributed to refractive errors, nutritional deficiencies, or psychosomatic causes, leading to delayed presentation to healthcare facilities. Cultural beliefs and stigma associated with

genetic disorders further hinder early diagnosis and acceptance of genetic counselling.

Inadequate Genetic Counselling and Family Screening

Genetic counselling services are underdeveloped in most developing countries. LHON, being maternally inherited with incomplete penetrance, requires detailed family counselling and screening of asymptomatic carriers. However, limited trained genetic counsellors, time constraints in busy clinics, and lack of awareness result in missed opportunities for preventive counselling. Family members at risk often remain unaware of lifestyle triggers such as smoking, alcohol consumption, and exposure to mitochondrial toxins, which can precipitate visual loss. This increases disease burden and reduces the potential for preventive strategies.

Nutritional and Environmental Risk Factors

Developing countries face a higher prevalence of nutritional deficiencies, chronic infections, and environmental toxin exposure, which may exacerbate mitochondrial dysfunction. Deficiencies in vitamins such as B12 and folate, along with oxidative stress from smoking or environmental pollutants, may influence disease penetrance and severity in LHON mutation carriers. Poor nutritional status may also negatively affect visual recovery and overall prognosis, further widening outcome disparities between developing and developed nations.

Psychosocial and Rehabilitation Challenges

Vision loss due to LHON often affects young individuals during critical educational and working years. In developing countries, rehabilitation services, low-vision aids, and vocational training programs are limited. Social security systems and disability benefits are often inadequate or inaccessible. Psychological support services are rarely integrated into ophthalmic care, leading to increased risk of depression, anxiety, and social isolation among affected individuals. The lack of structured support systems significantly impacts quality of life and long-term socioeconomic outcomes.

Limited Research and Clinical Trial Participation

Developing countries contribute minimally to global LHON research and clinical trials. Factors such as lack of research funding, absence of patient registries, and regulatory challenges limit participation in multinational studies. This results in underrepresentation of diverse genetic backgrounds, including unique mitochondrial haplogroups seen in Asian and African populations. Consequently, evidence-based management guidelines are often derived from Western populations, which may not fully reflect disease behaviour in developing

countries.

Health System and Policy Gaps

LHON is not commonly recognized as a public health priority in developing countries. The absence of national rare disease policies, lack of insurance coverage for genetic testing, and limited funding for orphan diseases further compound the challenges. Integration of LHON into national blindness prevention and rare disease programs remains limited.

Future Perspectives

Addressing LHON challenges in developing countries requires a multidimensional approach, including strengthening diagnostic infrastructure, improving access to genetic testing, enhancing awareness among healthcare professionals, and expanding genetic counselling services. Development of cost-effective diagnostic strategies, inclusion of LHON in rare disease frameworks, and participation in global research collaborations are essential to reduce disparities in care and outcomes.

LATE DIAGNOSIS REMAINS A SIGNIFICANT CHALLENGES IN LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

Clinical Overlap with More Common Optic Neuropathies

A major cause of delayed diagnosis in developed countries is the clinical overlap of LHON with more prevalent optic nerve disorders, particularly optic neuritis and non-arthritic anterior ischemic optic neuropathy (NAION). Young patients presenting with acute or subacute central vision loss are often initially presumed to have inflammatory or demyelinating optic neuritis, leading to early treatment with corticosteroids.

This misclassification is especially common in the early hyperaemic stage of LHON, when optic disc edema, peripapillary telangiectasia, and pseudo-edema can mimic inflammatory optic neuropathy. As a result, mitochondrial etiology may not be considered until visual recovery fails to occur, by which time irreversible retinal ganglion cell loss has already developed.

Overreliance on Neuroimaging and Exclusion-Based Diagnosis

In developed healthcare systems, extensive neuroimaging and laboratory testing are frequently performed to exclude compressive, inflammatory, or demyelinating causes of vision loss. While this approach is valuable, it can paradoxically delay LHON diagnosis by

reinforcing an exclusion-based diagnostic pathway, where genetic testing is considered only after all other causes are ruled out.

Normal or non-specific MRI findings may falsely reassure clinicians, leading to prolonged observation rather than early mitochondrial DNA analysis. This delay is critical, as therapeutic windows for interventions such as idebenone, or gene therapy are time sensitive.

Low Index of Suspicion in Sporadic Cases

Although family history is a key diagnostic clue, many LHON cases in developed countries present as apparently sporadic, due to incomplete penetrance and variable expression among maternal relatives. Absence of a known family history often lowers clinical suspicion for a hereditary optic neuropathy.

Additionally, asymptomatic carriers are common, and previous generations may have been misdiagnosed or never formally evaluated. This contributes to delayed recognition, particularly in patients without bilateral simultaneous involvement.

Gender Bias and Atypical Presentations

LHON predominantly affects young males, which can inadvertently contribute to diagnostic bias. Female patients, older individuals, or those with atypical disease progression may not be promptly evaluated for LHON. Slowly progressive or asymmetric visual loss is sometimes attributed to functional, toxic, or vascular causes, further delaying genetic confirmation.

Such atypical presentations are increasingly recognized but remain underrepresented in standard diagnostic algorithms, even in developed healthcare settings.

Delayed Genetic Testing Despite Availability

Although genetic testing is widely available in developed countries, delays in ordering mitochondrial DNA analysis remain common. This may stem from fragmented care pathways, where patients are evaluated sequentially by optometrists, general ophthalmologists, neurologists, and neuro-ophthalmologists before genetic testing is initiated.

Concerns about cost-effectiveness, insurance approval processes, and perceived rarity of LHON may further postpone testing. Consequently, genetic confirmation often occurs months after symptom onset, limiting treatment effectiveness and timely family counselling.

Limited Awareness of Treatment Time Sensitivity

Even when LHON is suspected, clinicians may underestimate the importance of early diagnosis for therapeutic intervention. Evidence suggests that treatments such as idebenone and gene therapy yield better outcomes when initiated during the early or subacute phase of the disease.

Late diagnosis results in missed opportunities for intervention during periods when retinal ganglion cells may still be viable, reducing the potential for visual recovery.

Fragmentation of Care in Specialized Health Systems

Highly specialized healthcare systems in developed countries may inadvertently contribute to diagnostic delays. Patients often undergo multiple referrals across subspecialties, resulting in prolonged diagnostic timelines. Lack of integrated mitochondrial disease clinics or standardized LHON diagnostic pathways further complicates early identification.

Psychological and Social Consequences of Delayed Diagnosis

Late diagnosis not only affects visual prognosis but also delays genetic counselling, lifestyle modification advice, and psychosocial support. Patients may continue exposure to risk factors such as smoking and alcohol consumption, which can worsen disease expression. Uncertainty during prolonged diagnostic periods also contributes to psychological distress and reduced quality of life.

FUTURE DIRECTIONS IN LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

Advances in mitochondrial biology, gene therapy, and neuroprotection have significantly transformed the research landscape of Leber's Hereditary Optic Neuropathy (LHON). However, important unmet needs remain. Future directions in LHON research and clinical care are expected to focus on early diagnosis, targeted molecular therapies, personalized medicine, and holistic patient management.

Earlier Diagnosis Through Precision Screening

Future strategies will prioritize earlier identification of LHON, particularly during the presymptomatic or subacute stages when therapeutic interventions are most effective. Integration of genetic screening for high-risk individuals, especially maternal relatives of affected patients, is likely to become standard practice.

Advances in retinal imaging biomarkers, including ganglion cell–inner plexiform layer (GC-IPL) analysis, adaptive optics, and artificial intelligence–assisted OCT interpretation, may enable detection of subtle preclinical changes before irreversible neuronal loss occurs. These tools could help stratify patients for early intervention and clinical trial enrolment.

Expansion and Optimization of Gene Therapy

Gene therapy represents the most promising disease-modifying approach for LHON. Future research will focus on:

Optimizing vector design to improve mitochondrial targeting efficiency and transgene expression

Bilateral and repeat dosing strategies to enhance and sustain visual recovery.

Extending gene therapy to non-ND4 mutations, including ND1 and ND6 variants

Long-term safety monitoring and real-world outcome data will be essential to define the durability of benefit and to guide regulatory approval and reimbursement decisions globally.

Emergence of Mitochondrial Gene Editing Technologies

Next-generation mitochondrial genome editing technologies, such as mitochondrial base editors and TALE-based systems, offer the potential for direct correction of pathogenic mitochondrial DNA mutations. Although currently at the preclinical stage, these approaches may eventually overcome limitations of allotropic gene expression and provide mutation-specific, permanent treatment options.

Continued development of safe and efficient mitochondrial delivery systems will be a key research priority before clinical translation becomes feasible.

Combination Therapies and Neuroprotection

Future LHON management is likely to involve combination treatment strategies, integrating gene therapy with: Mitochondrial antioxidants Neuroprotective agent Agents enhancing mitochondrial biogenesis and energy metabolism Such approaches may improve retinal ganglion cell survival, extend therapeutic windows, and enhance visual recovery, particularly in chronic stages of the disease.

Personalized Medicine and Genetic Modifiers

Understanding the role of mitochondrial haplogroups, nuclear genetic modifiers, epigenetic factors, and environmental triggers will be crucial for individualized risk prediction and

treatment planning. Personalized medicine approaches may allow stratification of patients based on likelihood of disease conversion, severity, and treatment response. This may also facilitate tailored lifestyle counselling and targeted preventive strategies for asymptomatic mutation carriers.

Global Collaboration and Inclusive Clinical Trials

Future progress in LHON research will depend on multinational collaborations and global patient registries to overcome the limitations imposed by disease rarity. Inclusion of diverse ethnic populations, particularly from underrepresented regions such as Asia and Africa, will enhance understanding of genotype–phenotype correlations and improve generalizability of clinical trial results. Standardization of outcome measures and harmonization of regulatory pathways will further accelerate therapeutic development.

Improved Access and Health Policy Integration

Bridging the gap between scientific advances and patient care will require policy-level interventions. Integration of LHON into national rare disease frameworks, improved insurance coverage for genetic testing and novel therapies, and expansion of specialized mitochondrial disease centers are critical future goals. Cost-effective diagnostic algorithms and tiered care models may help ensure equitable access to emerging treatments across both developed and developing countries.

Psychosocial Care and Vision Rehabilitation

Future care models will increasingly recognize the importance of holistic management, incorporating psychological support, low-vision rehabilitation, assistive technologies, and vocational training. Digital health platforms and tele-rehabilitation services may expand access to supportive care and improve long-term quality of life for affected individuals.

GENE THERAPY IN LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

Gene therapy has emerged as the most promising disease-modifying strategy for Leber's Hereditary Optic Neuropathy (LHON), addressing the underlying mitochondrial DNA mutations responsible for retinal ganglion cell degeneration. Unlike conventional treatments that provide metabolic or symptomatic support, gene therapy aims to restore mitochondrial function and preserve visual pathways.

Rationale for Gene Therapy in LHON

LHON is predominantly caused by point mutations in mitochondrial DNA, most commonly the m.11778G>A mutation in the ND4 gene, leading to impaired complex I activity and retinal ganglion cell apoptosis. Because mitochondrial DNA cannot be directly manipulated using conventional nuclear gene therapy techniques, LHON has driven the development of innovative approaches such as allotropic expression.

In allotropic expression, a wild-type version of the affected mitochondrial gene is delivered to the nucleus using a viral vector. The encoded protein is then targeted back to the mitochondria using a mitochondrial targeting sequence, thereby compensating for the defective mitochondrial gene.

Vector Design and Delivery

Most LHON gene therapy trials utilize adeno-associated virus (AAV) vectors, particularly AAV2, due to their favourable safety profile and strong tropism for retinal ganglion cells. The therapy is administered via intravitreal injection, allowing targeted delivery to the optic nerve head and inner retina. This minimally invasive route avoids systemic exposure and enables localized treatment of the affected tissue, making it particularly suitable for optic neuropathies.

Clinical Evidence and Key Advances

Clinical trials of ND4 gene replacement therapy have demonstrated:

Acceptable safety and tolerability, with no major vector-related adverse events Sustained improvement or stabilization of visual acuity in a subset of treated patients Unexpected bilateral visual improvement following unilateral injection, suggesting possible interocular or central nervous system-mediated effects These findings represent a paradigm shift in the management of hereditary optic neuropathies and provide proof of concept for mitochondrial gene therapy.

Timing and Therapeutic Window

One of the most critical factors influencing gene therapy outcomes is early intervention. Treatment during the acute or subacute phase, when retinal ganglion cells are still viable, appears to yield better functional outcomes. Late-stage disease, characterized by established optic atrophy, shows limited reversibility, highlighting the importance of early diagnosis and prompt referral.

Limitations and Challenges

Despite encouraging results, several challenges remain:

Current gene therapies primarily target ND4 mutations, limiting applicability to other LHON genotypes. Long-term durability of transgene expression and visual benefit requires continued monitoring. High cost and complex regulatory pathways restrict accessibility, particularly in developing countries. Standardization of outcome measures and patient selection criteria is still evolving.

Future Directions in LHON Gene Therapy

Future research is expected to focus on: Expanding gene therapy to non-ND4 mutations (ND1, ND6), Improving vector efficiency and mitochondrial targeting.

Exploring repeat or bilateral dosing strategies. Combining gene therapy with neuroprotective or metabolic treatments. Translating mitochondrial gene editing technologies from preclinical models to clinical use.

ADVANCEMENTS IN MITOCHONDRIAL MEDICINE AND THEIR IMPLICATIONS FOR (LHON)

Mitochondrial medicine has rapidly evolved from a largely descriptive discipline to a translational field with direct therapeutic relevance. These advances have profound implications for Leber's Hereditary Optic Neuropathy (LHON), a prototypical mitochondrial disorder, and are reshaping both disease understanding and management strategies.

Improved Understanding of Mitochondrial Pathophysiology

Recent advances have clarified the central role of mitochondrial bioenergetic failure, oxidative stress, and apoptotic signalling in LHON. Dysfunction of complex I leads to reduced ATP production and increased reactive oxygen species, triggering selective vulnerability of retinal ganglion cells. Recognition of mitochondrial–nuclear crosstalk and the influence of nuclear genetic modifiers has expanded the disease model beyond single mtDNA mutations. This has improved genotype–phenotype correlation and highlighted potential therapeutic targets outside the mitochondrial genome itself.

Advances in Mitochondrial Diagnostics

The development of next-generation sequencing (NGS) has transformed mitochondrial disease diagnostics. Comprehensive mitochondrial genome sequencing, combined with

nuclear gene panels, enables rapid and accurate detection of pathogenic variants, heteroplasmy levels, and modifier genes. Functional imaging advances, including high-resolution OCT, OCT angiography, and metabolic imaging, allow early detection of retinal ganglion cell dysfunction and monitoring of disease progression and treatment response. Artificial intelligence–based analysis is emerging as a tool for early diagnosis and risk stratification.

Mitochondria-Targeted Therapeutics

A major advancement in mitochondrial medicine is the development of mitochondria-targeted therapies. These include Antioxidants designed to localize within mitochondria. Agents that improve the efficiency of the electron transport chain. Compounds that enhance mitochondrial biogenesis and quality control. While many remain investigational, these therapies provide a mechanistic foundation for combination treatment approaches in LHON.

Gene Therapy and Allotropic Expression

Innovative gene therapy strategies, particularly allotropic expression of mitochondrial genes, represent a milestone in mitochondrial medicine. Successful nuclear delivery and mitochondrial targeting of ND4 in LHON have demonstrated that mitochondrial dysfunction can be therapeutically addressed despite the unique biology of mtDNA. These advances have validated mitochondria as viable targets for gene-based interventions and opened pathways for similar approaches in other mitochondrial disorders.

Mitochondrial Gene Editing Technologies

Emerging mitochondrial base editing platforms, including TALE-derived and deaminase-based systems, allow precise modification of mitochondrial DNA without double-strand breaks. Although still preclinical, these technologies offer the possibility of permanent correction of pathogenic mtDNA mutations, representing a potential paradigm shift in mitochondrial medicine. Successful clinical translation will depend on improvements in delivery efficiency, specificity, and long-term safety.

Personalized and Preventive Mitochondrial Medicine

Advances in mitochondrial genomics have enabled personalized risk assessment based on mtDNA haplogroups, heteroplasmy burden, and environmental modifiers. This is particularly relevant for LHON, where incomplete penetrance and variable expressivity complicate disease prediction. Preventive mitochondrial medicine now emphasizes lifestyle modification, early

carrier identification, and targeted counselling, aiming to reduce disease conversion among asymptomatic mutation carriers.

Integration into Multidisciplinary Care Models

Modern mitochondrial medicine increasingly adopts multidisciplinary care frameworks, integrating ophthalmology, neurology, genetics, psychology, and rehabilitation services. Digital health tools and telemedicine platforms are expanding access to specialist care and long-term monitoring, especially for rare mitochondrial disorders.

NEEDS FOR AN INDIAN LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

Leber's Hereditary Optic Neuropathy (LHON) is a rare mitochondrial disorder with significant visual, psychological, and socioeconomic consequences, particularly affecting young individuals during their most productive years. Despite India's large population and genetic diversity, systematic data on LHON remain sparse, highlighting the urgent need for a national Indian LHON registry.

Addressing the Epidemiological Data Gap

Currently, the true prevalence and incidence of LHON in India are unknown. Most available information originates from small, single-centre studies or isolated case series. An Indian LHON registry would enable accurate estimation of disease burden, regional distribution, age and gender patterns, and mutation frequencies, providing essential epidemiological insights relevant to the Indian population.

Understanding Indian-Specific Genetic Diversity

India harbours extensive mitochondrial haplogroup diversity, which may influence disease penetrance, severity, and visual recovery. A national registry would facilitate large-scale analysis of: Common and rare LHON-associated mtDNA mutations, Indian-specific haplogroups, and nuclear genetic modifiers, Genotype–phenotype correlations unique to Indian patients. Such data are critical for understanding why disease expression and outcomes may differ from those observed in Western cohorts.

Improving Early Diagnosis and Referral Pathways

Delayed diagnosis is a major challenge in India due to limited awareness and access to genetic testing. A registry can support standardized diagnostic criteria, promote early referral to tertiary centers, and facilitate the development of national clinical pathways. Registry-

based data can also help identify gaps in healthcare access across urban and rural regions.

Enabling Access to Emerging Therapies and Clinical Trials

Global clinical trials in LHON, particularly gene therapy studies, require well-characterized patient cohorts. An Indian LHON registry would:

Enable rapid identification of eligible patients for international and indigenous clinical trials
Improve India's representation in global research
Support future gene therapy access and regulatory approvals within the country. This is especially important as gene-based treatments move toward wider clinical use.

Strengthening Genetic Counselling and Preventive Care LHON exhibits maternal inheritance with incomplete penetrance, making family screening and counselling essential. A registry would facilitate:
Identification of at-risk family members
Long-term follow-up of asymptomatic mutation carriers
Evaluation of lifestyle and environmental risk factors such as smoking and alcohol use. This would support preventive strategies aimed at reducing disease conversion rates.

Assessing Visual Outcomes and Real-World Management

An Indian registry would allow longitudinal tracking of:
Natural history of LHON in Indian patients.
Visual outcomes with and without treatment.
Real-world use and effectiveness of therapies such as idebenone. Such outcome data are crucial for developing India-specific management guidelines and health-economic evaluations.

Informing Health Policy and Rare Disease Planning

Inclusion of LHON in India's rare disease framework requires robust data. Registry-generated evidence can support:
Policy advocacy for insurance coverage of genetic testing and treatments.
Allocation of resources for low-vision rehabilitation and disability support
Integration of LHON into national blindness prevention and rare disease programs.

Fostering Multicentre Collaboration and Capacity Building

A national LHON registry would promote collaboration among ophthalmologists, neurologists, geneticists, and researchers across India. It would also serve as a platform for training, standardization of care, and capacity building in mitochondrial medicine and neuro-ophthalmology.

CONCLUSION

LEBER'S HEREDITARY OPTIC NEUROPATHY (LHON)

Leber's Hereditary Optic Neuropathy (LHON) remains a devastating mitochondrial disorder that predominantly affects young individuals, leading to irreversible visual loss and profound psychosocial and socioeconomic consequences. Although LHON is genetically well characterized, significant challenges persist in timely diagnosis, equitable access to advanced diagnostics, and effective disease-modifying treatment across both developed and developing countries.

Recent advances in mitochondrial medicine and gene therapy have fundamentally transformed the therapeutic landscape of LHON. Allotropic gene expression strategies, emerging mitochondrial gene editing technologies, and mitochondria-targeted therapies offer realistic hope for altering the natural course of the disease, particularly when intervention occurs early. However, the benefits of these innovations are currently limited by late diagnosis, high treatment costs, and unequal global access.

In the Indian context, gaps in epidemiological data, limited genetic testing availability, and low disease awareness highlight the urgent need for structured national initiatives, including the establishment of an Indian LHON registry. Such efforts would enable better understanding of population-specific genetic factors, improve early diagnosis and counselling, and facilitate participation in global clinical trials.

Moving forward, progress in LHON management will depend on early genetic confirmation, multidisciplinary care models, global research collaboration, and health-policy integration of rare diseases. Bridging the gap between scientific innovation and real-world patient care is essential to ensure that emerging therapies translate into meaningful visual and quality-of-life benefits for individuals affected by LHON worldwide.

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