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ORIGINAL ARTICLE

Late-Onset Leber Hereditary Optic Neuropathy: A Case Series of 16 Patients Diagnosed Above 65 Years of Age

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ABSTRACT

Leber hereditary optic neuropathy (LHON) is a mitochondrial optic neuropathy that typically affects young adult males. Late-onset disease is rare and often underrecognised. We conducted a retrospective case series of patients aged > 65 years at onset of visual loss diagnosed with LHON between 2004 and 2025 at two tertiary referral centers in Belgium and the Netherlands. Demographics, genetic mutations, environmental and systemic risk factors, visual outcomes, and response to idebenone were analyzed. Best-corrected visual acuity was assessed at presentation, nadir, and >1 year after onset. Treatment response was defined according to criteria for clinically relevant recovery. Sixteen male patients were included, with a mean age of onset of 72.8 years. The most frequent mutation was MT-ND4 (m.11778 G > A), followed by MT-ND6 (m.14484T > C) and MT-ND1 (m.4135T > C). Seven patients reported a family history, none had a symptomatic mother. Visual loss was severe at presentation in most cases. Twelve patients received idebenone therapy, with clinically relevant recovery observed in half. However, final visual acuity remained poor in the majority. Risk factors were common, including smoking, high-risk alcohol use, diabetes mellitus, and glaucoma. Late-onset LHON is a clinically relevant but underrecognised phenotype, likely reflecting interplay between genetic susceptibility, cumulative exposures, comorbidities, and age-related mitochondrial dysfunction. Increased awareness is needed for timely diagnosis and management in elderly patients with unexplained optic neuropathy.

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Leber hereditary optic neuropathy; late-onset; genetic and environmental risk factors; mitochondrial disease; Idebenone treatment

Introduction

Leber hereditary optic neuropathy (LHON) is a rare genetic disorder that affects the optic nerve through mitochondrial dysfunction. It is characterized by sequential, often irreversible, painless loss of central vision.[1] The disease typically begins with a subacute unilateral visual decline. Within approximately 4 to 6 weeks, the patient develops a large, dense cecocentral scotoma in that eye. Involvement of the fellow eye usually occurs several weeks to months later. In the subacute phase, a hyperemic optic disc, pseudoedema with swelling of the retinal nerve fiber layer, telangiectatic microangiopathy, and retinal vascular tortuosity may be observed. Eventually, this progresses into optic nerve atrophy with pallor in the chronic phase, over 6 months after the initial symptoms.[2]

The primary etiologic factor of the disease is a point mutation in the mitochondrial DNA (mtDNA), affecting complex I (CI) subunit genes in the respiratory chain, leading to selective degeneration of retinal ganglion cells (RGCs) and optic atrophy.[2,3] Approximately 90% of cases are attributable to one of three primary mutations: m.11778 G.A > MT-ND4, m.3460 G.A > MT-ND1, and m.14484T.C > MT-ND6.[4] Most of these pathogenic variants are homoplasmic, but heteroplasmy has also been reported in 10–15% of LHON cases.[3] Recently, it was discovered that certain variants in the nuclear gene DNAJC30 can result in an autosomal recessive form of LHON.[5] DNAJC30 functions as a chaperone protein, facilitating the exchange of damaged CI subunits. Patients with autosomal recessive LHON typically present at a younger age and usually respond better to treatment with idebenone than the mitochondrial inherited group.[5]

LHON can affect both men and women, with a higher prevalence in males. The average age of

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onset is between 15 and 35 years. Although cases have been reported in both younger and older individuals, late-onset disease remains uncommon.[5] In this case series, we present 16 male patients diagnosed with new onset LHON at an atypically advanced age (>65 years) diagnosed at University Hospitals of Leuven (Belgium) and Rotterdam Eye Hospital (the Netherlands). We describe their demographics, risk factors, clinical as well as genetical picture and propose hypotheses regarding potential mechanisms underlying this late-onset disease expression.

Materials and methods

This retrospective review examined the medical records of all patients aged over 65 years who were diagnosed with new onset LHON between 2004 and 2025 at the University Hospitals of Leuven and Rotterdam Eye Hospital. The primary outcomes of this study were best corrected visual acuity (BCVA) at baseline, BCVA at nadir and more than one year after onset (Tables 1 and 2). BCVA was assessed using the Snellen visual acuity chart. In some patients, visual acuity was also measured using the ETDRS chart. For the patients recruited in Leuven, only Snellen measurements were available. These were converted to ETDRS letter scores using a standardized formula (supplementary methods). BCVA between nadir and the last follow-up visit was compared to determine whether there was a clinically relevant recovery (CRR) during idebenone treatment. CRR was defined as an improvement from below chart level (i.e., >1.68 logMAR) to within chart range (1.60 logMAR or better, corresponding to a gain of 5 ETDRS letters), or as an improvement of at least 0.20 logMAR (equivalent to 10 ETDRS letters) for patients who were already within chart range.[6] Clinical relevant stabilization (CRS) was defined as maintaining a BCVA of <1.0 logMAR in at least one eye at baseline, with this level of visual function preserved in the same eye through the last visit. The type of mitochondrial mutation was described. In addition, environmental and lifestyle factors including alcohol consumption, smoking, medication abuse, as well as family history were evaluated (Table 3). This retrospective study was approved by the Ethical Committee Research of the University Hospitals of Leuven with reference number S71090. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and applicable data protection regulations. Given the retrospective design of the study and the use of pseudonymized data, the requirement for informed consent to participate was waived by the ethics committee. A data transfer agreement was signed to exchange pseudonymized data between both centers.

Results

A total of 16 patients were included with a mean age of 72.8 years. All of them were male. Across both participating centers, the total number of diagnosed patients during the respective study period was also assessed for context. In Leuven, 42 patients were

Table 1. Visual outcomes.

	BCVA at baseline visit OD/OS	BCVA at Nadir OD/OS			BCVA at last visit (>1y after onset) OD/OS		
	Snellen	Snellen	ETDRS	LogMAR	Snellen	ETDRS	LogMAR
Case							
1	<0.05/0.3	CF/HM	0/0	2.0/2.3	CF/HM	0/0	2.0/2.3
2	0.1/CF 2 m	CF/HM	0/0	2.0/2.3	CF/ CF	0/0	2.0/2.0
3	0.6/CF 1.5 m	CF/CF	0/0	2.0/2.0	CF /CF	0/0	2.0/2.0
4	CF 2 m/0.3	CF/CF	0/0	2.0/2.0	CF/ CF	0/0	2.0/2.0
5	0.25/0.6	/	/	/	/	/	/
6	CF 3 m/CF 1 m	CF/ CF	0/0	2.0/2.0	Unknown	n.a./ n.a.	n.a./ n.a.
7	CF 2 m/CF 2 m	CF/ CF	34/30	1.02/1.1	0,4/0,25 (2017)	64/55	0.42/0.6
8	0,2/0,5	HM/ CF	0/12	2.3/1.46	CF/ CF (2024)	9/14	1.52/1.42
9	CF 0,5 m/CF 0,5 m	HM//HM	9/9	1.52/1.52	0,1/0,15 (2025)	48/53	0.74/0.64
10	CF 0,5 m/CF 1 m	LP /LP	0/0	2.6/2.6	CF/ HM(2025)	27/7	1.16/1.56
11	0,05/CF 1 m	HM/HM	0/0	2.3/2.3	HM/CF	11/23	1.48/1.24
12	0.03/0.02	HM/ HM	0/2	2.3/1.66	HM/HM	0/5	2.3/1.6
13	0,7/CF 1 m	LP /LP	0/0	2.6/2.6	HM/HM(2025)	1/1	1.68/1.68
14	0,12/0,3	1/300/2/300	0/1	1.7/1.68	0,2/2/60 (2025)	47/28	0.76/1.14
15	1/60/1/60	n.a./ n.a.	n.a./ n.a.	n.a./ n.a.	0,05/0,5/60 (2010)	1/0	1.68/1.7
16	1/60/1/60	n.a./ n.a.	n.a./ n.a.	n.a./ n.a.	0,1/0,1 (2009)	5/5	1.6/1.6

HM = hand movements. CF = counting fingers. LP = light perception.

Table 2. Determination of CRR.

	BCVA at Nadir OD/OS		BCVA at last visit (>1y after onset) OD/OS		Idebenone treatment	Duration of treatment	CRR
	ETDRS	LogMAR	ETDRS	LogMAR			
Case							
1	0/0	2.0/2.3	0/0	2.0/2.3	Yes	since 10/2023	No
2	0/0	2.0/2.3	0/0	2.0/2.0	Yes	since 07/2024	No
3	0/0	2.0/2.0	0/0	2.0/2.0	Yes	since 06/2024	No
4	0/0	2.0/2.0	0/0	2.0/2.0	Yes	since 06/2024	No
5	/	/	/	/	Not yet	/	/
6	0/0	2.0/2.0	n.a./ n.a.	n.a./ n.a.	No	/	/
7	34/30	1.02/1.1	64/55	0.42/0.6	Yes	Yes,10/2015–07/2016	Yes
8	0/12	2.3/1.46	9/14	1.52/1.42	Yes	Yes, 01/2018–11/2019	Yes (one eye)
9	9/9	1.52/1.52	48/53	0.74/0.64	Yes	Yes, 01/2021–08/2024	Yes
10	0/0	2.6/2.6	27/7	1.16/1.56	Yes	Yes, 08/2022–01/2025	Yes
11	0/0	2.3/2.3	11/23	1.48/1.24	Yes	Yes, 05/2023–03/2025	Yes
12	0/2	2.3/1.66	0/5	2.3/1.6	Yes	Yes, since 07/2024	No
13	0/0	2.6/2.6	1/1	1.68/1.68	Yes	Yes, since 09/2023 till 09/2025	No
14	0/1	1.7/1.68	47/28	0.76/1.14	Yes	Yes, since 12/2016 till 03–2018	Yes
15	n.a./ n.a.	n.a./ n.a.	1/0	1.68/1.7	No	/	/
16	n.a./ n.a.	n.a./ n.a.	5/5	1.6/1.6	No	/	/

CRR = clinically relevant recovery.

Table 3. Demographics, genetic and environmental factors.

Case	Age at onset	Sex	Mutation	Familial history	Smoking	Alcohol	Diabetes Mellitus	Open angle glaucoma
1	73	Male	MT-ND4 (m.11778 G > A)	No	Light	No	No	No
2	85	Male	MT-ND6 (m.14484T > C)	No	No	Unknown	No	No
3	77	Male	MT-ND4 (m.11778 G > A)	No	Heavy	Low risk	No	No
4	83	Male	MT-ND1(m.4135T > C)	Sister LHON suspect	Unknown	Unknown	No	No
5	68	Male	Genetic analysis in progress	Unknown	No	No	Yes, type 2	No
6	70	Male	MT-ND4 (m.11778 G > A)	No	Light	High risk	No	No
7	70	Male	MT-ND6 (m.14484T > C)	Yes (3/3 brothers, 2/3 sisters LHON suspect)	Heavy	High risk	Yes, type 2	No
8	75	Male	MT-ND6 (m.14484T > C)	Yes, second cousin	No	High risk	Yes, type 2	No
9	77	Male	MT-ND4 (m.11778 G > A)	No	No	High risk	No	Yes
10	70	Male	MT-ND4 (m.11778 G > A)	Yes (uncle, nephew)	Moderate	High risk	No	No
11	73	Male	MT-ND4 (m.11778 G > A)	Yes (3 uncles LHON suspect)	Heavy	High risk	No	Yes
12	75	Male	MT-ND4 (m.11778 G > A)	Yes (2 nieces)	Smoking cessation at 45 y/o	High risk	Yes, type 1	No
13	68	Male	MT-ND4 (m.11778 G > A)	No	No	Low risk	No	No
14	69	Male	MT-ND4 (m.11778 G > A)	Yes	Heavy	Low risk	No	Yes
15	65	Male	MT-ND4 (m.11778 G > A)	No	Light	Low risk	No	Yes
16	67	Male	MT-ND4 (m.11778 G > A)	No	Light	High risk	No	No

Moderate smoking (10–20/day), heavy smoking (>20/day). Alcohol (according to the NHS criteria): low-risk (<14 units/week); high-risk (>14 units/week).

diagnosed with LHON between 2004 and 2025, of whom approximately 9.5% were older than 65 years. In Rotterdam, only exact data between 2016 and 2024 were available. 110 patients were diagnosed in that period, of whom 13 patients were older than 65 years, corresponding to approximately 11.8%.

Seven patients reported a family history of LHON. However, none of the affected patients had a symptomatic mother. One patient was recently included in the late-onset LHON group. Therefore, detailed genetic analysis and follow-up data of this patient are not yet available. Among the remaining

patients, one carried the MT-ND1 (m.4135T > C) mutation, while three harbored the MT-ND6 (m.14484T > C) mutation. The MT-ND4 (m.11778 G > A) mutation was identified in eleven patients. Two of the three patients with the MT-ND6 (m.14484T > C) mutation demonstrated a CRR. The remaining patient without CRR was from the Leuven cohort, in whom ETDRS visual acuity measurements were not available. At baseline visit in our clinics, BCVA was already severely reduced in one or both eyes in nearly all patients: 5/16 (31.2%) presented with a BCVA < 0.1 (Snellen) in one eye, 8/16 (50.0%) already in both eyes (Table 1). Only 3/16 (18.8%) had a measurable visual acuity of ≥0.1 (Snellen) in both eyes. The nadir visual acuity, when available, typically reached hand movements or worse, reported in 8 patients (50.0%).

Twelve patients received idebenone (Raxone) treatment. To assess the clinical response to this therapy, visual acuity measurements at nadir were compared with those at the last follow-up visit. For patients from the Rotterdam cohort, visual acuity was assessed using both Snellen and ETDRS charts. Because these patients had very poor vision, the ETDRS low-vision protocol was applied. Testing was first performed at 4 meters and, if unsuccessful, continued at 1 meter. The number of letters read at 1 meter was then used to derive the ETDRS letter score. In contrast, patients from the Leuven cohort did not undergo ETDRS testing, and only Snellen visual acuity was available. Therefore, improvements detectable with the ETDRS low-vision protocol, particularly at a testing distance of 1 meter, could not be captured in these patients, limiting direct comparison with the Rotterdam cohort.

Based on the ETDRS letter scores, 6 out of 12 patients (50.0%) or 11 eyes demonstrated a CRR. No patients showed CRS. There was one lost to follow-up. It is important to note that in 11 patients, or 21 eyes, logMAR visual acuity remained low (>1.0 logMAR) at the last visit, despite CRR being present in 6 patients compared to nadir. This apparent discrepancy is explained by the ETDRS low-vision testing protocol. Several patients were able to identify additional ETDRS letters when tested at 1 meter rather than 4 meters, resulting in an increase in ETDRS letter score that fulfilled the definition of CRR, while their overall visual acuity remained within the severe visual impairment range.

Regarding smoking habits, 5 patients (31.3%) were nonsmokers, 4 (25.0%) were light smokers, 1 (6.3%) was a moderate smoker, and 4 (25.0%) were heavy smokers. Light smoking was defined as consuming up to 20 cigarettes per day, while heavy smoking was defined as consuming more than 20 cigarettes per day.[7] Two patients had an unknown smoking status. In total, approximately 56% of patients had a history of tobacco use. With respect to alcohol consumption, 8 patients (50.0%) were classified as high-risk drinkers (>14 units per week), 4 (25.0%) as low-risk drinkers (≤14 units per week), 3 patients (18.8%) reported no alcohol intake, and 1 (6.3%) had unknown alcohol status. The alcohol consumption thresholds were based on the National Health Service (NHS) guidelines.[8] Diabetes mellitus was present in 5 patients (31.3% of the cohort), and open-angle glaucoma was diagnosed in 3 patients (18.8%).

Discussion

We present 16 cases of newly diagnosed late-onset LHON above the age of 65 with their phenotypic and genetic characteristics. Our findings highlight several important aspects regarding the late-onset presentation of LHON. The occurrence of new onset disease in elderly patients, as observed in our cohort, is rare and underscores the broad phenotypic variability of mitochondrial disorders.[3] While most patients carried the common MT-ND4 (m.11778 G > A) mutation, variants in MT-ND6 (m.14484T > C) and MT-ND1 (m.4135T > C) were also observed, indicating that both primary and rarer LHON mutations can present well beyond the typical age of onset. Our observations are in line with the conceptual framework proposed by Carelli et al., who distinguished between a predominantly genetic, early-onset form of LHON (type I) and a later-onset form in which environmental factors play a major triggering role (type II).[9] In their study, late-onset LHON was frequently associated with cumulative toxic exposures, particularly tobacco use, and demonstrated a more insidious clinical course, supporting the view that late-onset disease reflects a gene-environment interaction rather than a purely genetically determined process. Nevertheless, we found a rather acute loss of vision of both eyes sequentially in our case series.

In our cohort of patients, more than half received idebenone therapy, with 50.0% demonstrating a clinically relevant recovery. These findings suggest that, although idebenone may offer functional benefit even in elderly individuals, the overall therapeutic response in late-onset disease appears modest compared with younger cohorts described in the literature.[6,10,11]

Lifestyle and systemic risk factors were highly prevalent, which may have contributed to disease expression in this age group. Approximately 56% of patients had a history of tobacco use, and half of them were classified as high-risk alcohol consumers.

Both are well-established environmental modifiers that may lower the threshold for visual loss in mitochondrial optic neuropathies.[12] In addition, metabolic and ocular comorbidities such as diabetes mellitus (31.3%) and open-angle glaucoma (18.8%) were common, potentially exacerbating mitochondrial stress and RGC vulnerability.

Interestingly, although seven patients reported a family history of LHON, none of the patients' mothers were symptomatic. This observation may reflect incomplete penetrance, variable expression, or a lack of recognition of prior cases, further underscoring the complex interplay between genetic predisposition and environmental modifiers in LHON pathogenesis.

The mechanisms underlying late-onset disease expression remain insufficiently understood, but several factors may contribute. Late manifestation likely reflects a delayed crossing of a critical vulnerability threshold in RGCs. A recent study by Takai et al. demonstrated that acute-phase RNFL swelling is significantly less prominent in older LHON patients.[13] This attenuated swelling response may be explained by age-related loss of retinal ganglion cells and axons, reduced axonal transport capacity, and diminished mitochondrial reserve, resulting in a blunted acute optic disc swelling. Age-related mitochondrial dysfunction increased oxidative stress, and cumulative exposure to environmental or metabolic insults may progressively erode neuronal resilience, allowing pathogenic mtDNA mutations to become clinically manifest only later in life. Compensatory mechanisms such as mitochondrial biogenesis may initially preserve visual function but ultimately fail with aging or sustained toxic exposure.[9] Together, these observations support the notion that late-onset LHON arises from a multifactorial interplay between genetic susceptibility, lifetime exposures, and age-related mitochondrial deterioration.

In older patients, maintaining a high index of suspicion and considering LHON within a broad differential diagnosis remain essential to ensure timely recognition and management.

This study has several limitations. The retrospective design and relatively small sample size limit the generalizability of our findings. Visual acuity data were not uniformly collected across all patients. For several individuals, BCVA was originally measured using the Snellen chart and subsequently converted to ETDRS letter scores. Although commonly applied in clinical research, such conversions introduce variability, as Snellen and ETDRS measurements are not fully interchangeable and may differ in sensitivity and precision. This heterogeneity in visual acuity assessment may therefore have influenced the accuracy of comparisons between visits and across patients. Furthermore, the absence of standardized imaging or functional testing precludes detailed correlation with structural optic nerve changes.

In conclusion, LHON can manifest at advanced age with severe visual impairment, predominantly in male patients carrying common mtDNA mutations. Visual prognosis is generally poor, and therapeutic response to idebenone appears limited in this age group. Environmental exposures, systemic comorbidities, and age-related mitochondrial decline likely contribute to late-onset disease expression. We emphasize the need for heightened clinical awareness and consideration of environmental and systemic risk factors in elderly patients presenting with unexplained optic neuropathy. Recognizing these cases is critical for accurate diagnosis, genetic counseling, and management of at-risk family members.

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Dr. Kato Putcuijps performed the data analysis and wrote the manuscript. Dr. Lushchyk and Prof. Cassiman collected the clinical data from their respective institutions and critically revised the manuscript. Prof. Van Everdingen reviewed the final manuscript, together with Prof. Cassiman and Dr. Lushchyk. All authors approved the final version.

Author contributions

CRediT: **Kato Putcuijps:** Investigation, Methodology, Writing – original draft, Writing – review & editing; **Tanya Lushchyk:** Supervision; **Catherine Cassiman:** Supervision; **Judith Van Everdingen:** Supervision.

Supplementary methods

Snellen to ETDRS conversion

- ETDRS letters = (1.7 – logMAR) / 0.02[14]

Snellen to LogMAR conversion

- LogMAR = $-\log_{10}$(decimal Snellen visual acuity)

ETDRS to LogMAR conversion

- LogMAR = 1.7 – (0.02 × ETDRS letters)

LogMAR equivalents

- Counting fingers = 2.0 LogMAR
- Hand movements = 2.3 logMAR
- Light perception = 2.6 logMAR[13]

Disclosure statement

No potential conflict of interest was reported by the author(s).

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