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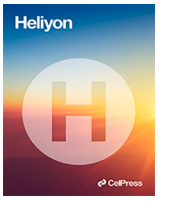

Research article

Leber hereditary optic neuropathy in Czechia and Slovakia: Quality of life and costs from patient perspective

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A R T I C L E I N F O

Keywords:
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A B S T R A C T

Introduction: Leber hereditary optic neuropathy (LHON) is the most frequent mitochondrial disease causing dyschromatopsia and progressive central visual loss that is subacute in progression and painless. Several studies have been published assessing QoL in patients with LHON, but no estimate of the economic burden has been reported to date. This study aims to quantify direct non-medical and indirect costs (productivity loss) incurred by LHON patients and their informal caregivers in Czechia and Slovakia, as well as to assess their quality of life.
Methods: The study was performed in 27 adults and children with LHON. To determine the socioeconomic burden of LHON, separate questionnaires for adults, children, and their parents were developed, including demographic and socioeconomic data. The following data were collected: age, education, family size, severity of LHON, non-medical direct and indirect costs of LHON.
Results: The mean age of adult respondents was 36.1 years (SD 13.1; n = 21). The total cost of absenteeism was EUR 1003 per person/year in adult employees, and EUR 2711 per person/year in children's parents. The productivity loss as a consequence of LHON due to combined relative absenteeism and relative presenteeism was estimated at EUR 9840 per an adult patient/year, and EUR 6298 per a parent/year, respectively. The mean cost of informal care was estimated at EUR 4502 (SD 4772; n = 6) per person/year. The mean VFQ-25 score for adult patients with LHON was 43.47 (SD 15.86).
Conclusion: The results of this study clearly show that patients with LHON and their families face an extensive socioeconomic burden related to this rare disease. Early, timely and appropriate access to diagnosis, treatment, and reimbursement decisions, but also to psychological

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counselling and services may help the patients and their relatives adapt and cope with the challenging aspects of vision loss and life with the disease.

1. Introduction

Leber hereditary optic neuropathy (LHON) is the most frequent mitochondrial disease causing dyschromatopsia and progressive and painless central visual loss. Both eyes are affected simultaneously in about 25–50 % of cases. The majority of patients are young adults with the peak of onset in the second and third decades of life. Males are five times more affected than females [1–3]. More than 90 % of patients with LHON have one of three primary point mitochondrial mutations (m.3460G > A, m.11778G > A, and m.14484T > C) [4–6]. These mutations affect complex I (NADH-ubiquinone oxidoreductase) of the mitochondrial respiratory chain, causing energy production failure and cell death [6]. Mutations are clinically silent until some unknown factors induce disease manifestation [7].

LHON is classified as a rare disease with a prevalence of 1:30,000 to 1:54,000 in Europe [8–11]. However, the frequency of individuals with confirmed mutations including asymptomatic carriers is estimated to be up to 1:8500 [11,12]. Published data about prevalence and incidence in the Czechia and Slovakia are missing. In Czechia, over 90 individuals with one of three prevalent mutations were diagnosed between 1992 and 2016 at the Institute of Inherited Metabolic Disorders of the First Faculty of Medicine, Charles University and General University Hospital, Prague, of which 20 patients were symptomatic [13]. In Slovakia, 13 symptomatic patients were diagnosed with LHON at the Department of Paediatric Ophthalmology of the Faculty of Medicine, Comenius University Bratislava, and the National Institute of Children's Diseases since 2005 (unpublished data).

The functional prognosis is generally poor, and the severity of visual loss depends on the duration between the onset of LHON symptoms and the initiation of treatment. Currently there is no treatment that could prevent the manifestation of LHON or fully recover vision functions. Idebenone (synthetic analogue of coenzyme Q10) is the first-line treatment approved for patients with LHON. Real-world data have demonstrated the benefit of idebenone treatment in recovering lost vision and maintaining good residual vision in non-chronic patients. The treatment should be initiated early (<1 year since the onset of the disease) at a dose of 900 mg/day for at least 24 months to maximize the efficacy. There is no significant improvement of visual acuity in chronic patients (over one year after the onset in the second eye) after idebenone treatment [7,14–16].

Manifesting LHON, similarly to other vision impairments, may result in a significant social and economic burden for patients and their families. As a consequence of decreased productivity and quality of life (QoL), the disease imposes considerable non-medical and indirect costs in addition to medical costs [17–20]. Several studies assessed QoL in patients with LHON, but no estimate of the economic burden has been published to date. This study aims to quantify direct non-medical and indirect costs (productivity loss) incurred by the LHON patients and their informal caregivers in Czechia and Slovakia, as well as to assess their QoL.

2. Materials and methods

2.1. Landscape mapping

Prior to patient data collection, in-depth face-to-face interviews with key opinion leaders (KOLs) and/or specialists on LHON from the Czechia and the Slovakia were conducted to get a deep insight and perspective on the disease, including availability of diagnosis and treatment, patient journey, patients' number etc.

2.2. Ethical approval and informed consent

The study was approved by the Ethics Committee of the National Institute of Children's Diseases, Slovakia under the number EK/5/2022 on May 24, 2022, and by the Ethics Committee of the General University Hospital in Prague under the number 102/22S on June 21, 2022. All participants or their parents or legal representatives signed a written informed consent, and we also have assent from minors.

2.3. Study design

The study was performed in the Czechia and Slovakia. Data were collected from 27 adults and children with LHON. To determine the socioeconomic burden of LHON, separate questionnaires for adults, children, and their parents were developed, including demographic and socioeconomic data. The centres recruited patients through their treating physician, and all LHON patients in the centres' database were offered voluntary participation in the study. The analysis was conducted on the responses of 27 patients who agreed to participate and completed an anonymous online questionnaire. The following data were collected: age, education, family size, onset of LHON, severity of LHON, non-medical direct and indirect costs of LHON. Direct non-medical costs included out-of-pocket payments for transportation, education, informal care (adult patients), visual aids and modifications of domestic environment. These costs were calculated based on the survey results. Indirect costs (productivity loss of patients or paediatric patients' parents) were calculated as absenteeism and presenteeism according to the World Health Organization's Heath and Work Performance Questionnaire (HPQ) [21]. Absenteeism refers to "absence from work due to health problems," while presenteeism is defined as "health-related

productivity loss while at paid work".

Furthermore, data on the quality of life were collected. National Eye Institute 25-item Visual Function Questionnaire (VFQ-25, version 2000) for adults [22] and Paediatric Eye questionnaire (PedEyeQ, version 2019) for children and their parents were used [23]. The VFQ-25 consists of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. The VFQ-25 subscale scores are the average of the list-items in the subscale transformed to a 0 to 100 scale, where 100 represents the best possible score on the measure and 0 represents the worst. The composite VFQ-25 score is an unweighted average of the responses to all list-items except for the general health rating question [22]. VFQ-25 questionnaire was previously psychometrically validated for the use in Slovakia [24]. The Paediatric Eye Questionnaire (PedEyeQ) has been developed to assess the impact of childhood eye conditions on child's eye-related quality of life and functional vision for children aged 0–17 years and their parents. Each of the child, proxy, and parent domains are independent of each other. Therefore, the domains may be administered independently, along with their included instructions. Scores were converted using a linear transformation, anchoring the extremes of the Rasch range for each domain at 0 (worst) and 100 (best) [23,25].

2.4. Data collection and analysis

Data were collected using electronic data capture system (CLADE-IS). All data collected via CLADE-IS were reviewed by data managers of CEEOR for clarity and completeness. A descriptive data analysis was performed primarily on all variables of interest. Ordinary and category variables were analysed by frequencies. All metric data were described by the mean, standard deviation, median, minimum and maximum. Linear correlation and unpaired *t*-test were used to assess whether the duration of LHON could affect the measured outcomes of indirect costs and quality of life. The absenteeism was scored in terms of hours lost per month, which means that a higher score indicates a higher amount of absenteeism. We calculated the monetary value for a working hour among patients/parents, who were absent due to LHON and then multiplied by the number of missed workhours to estimate the absenteeism cost. The relative presenteeism was calculated as a ratio of actual performance to the performance of most workers at the same job. Productivity losses were evaluated as human capital approach (HCA), which expresses the loss as the product of missed workhours multiplied by national mean hour gross wages (EUR 10.25) in 2021. All costs were converted to 12/2021-11/2022 mean EUR conversion rate (EUR 1 = CZK 24.6499).

The cost of informal care of adult patients was calculated using the opportunity cost method, i.e. the number of hours missed from work by informal caregivers was multiplied by their hourly wage.

Analyses were performed by the SAS 9.4 software, version TS Level 1M7 X64_10PRO platform.

3. Results

3.1. Mapping the landscape

Below, we summarize deep insight and perspective on the disease, including centres, number of patients, diagnosis, reimbursement system and treatment collected from local KOLs in Slovakia and Czechia (Table 1).

3.1.1. Epidemiology

Of the 27 patients with LHON included in the study, 21 (77.8 %) were adults and 6 (22.2 %) were children. The mean age of adult respondents was 36.1 years (SD 13.1, 25 % percentile 26.5 years; 75 % percentile 45.5 years). Mean age of children was 13.8 (SD 1.83).

As concerns the most frequent level of visual impairment measured by a self-assessment, the patients reported "some useful peripheral vision", followed by "good peripheral vision" and "moderate peripheral vision loss" (Table 2). Eighty-five percent (n = 23) of patients, both adults and children, were treated with idebenone.

Table 1
Landscape mapping of LHON in Slovakia and Czechia.

	Slovakia	Czechia
Centre for LHON treatment	Centre for Rare Diseases at NDUCH in Bratislava (for paediatric patients); Centre at the Saint Michael's Hospital, Bratislava	Department of Ophthalmology and Department of Paediatrics and Inherited Metabolic Disorders, General University Hospital in Prague, which are part of the ERN-EYE and MetabERN (European Reference Networks)
No of patients in center's database	11 genetically confirmed and symptomatic	150 genetically confirmed/51 symptomatic
Time to diagnosis	6–12 months from the onset of LHON	2 months from the onset of LHON
Diagnostic markers	Genetic confirmation/SD-OCT	Genetic confirmation/SD-OCT/visual acuity
Reimbursement system of idebenone (Raxone)	Reimbursed upon individual approval	Reimbursement within the National health care system
Treatment	Treatment initiated within 6 months from the onset of LHON as a standard, but approval process of health insurance company can take 1–3 months (depending on the health insurance company)	Treatment initiated within 6 months from the onset of LHON

Abbreviations: NDUCH (National Institute of Children's Diseases), SD-OCT (Spectral Domain Optical Coherence Tomography).

3.1.2. Loss-of-productivity costs

Thirty-eight percent of adult patients were on disability pension, and 14 % of them were employed part time due to LHON. Only 24 % of adult patients had a full-time job (Table 3). Employed adult patients (full- or part-time job) lost only 6 % of their working time, which represented an average of 97.8 working hours missed per year, as compared with parents of children, who lost 29 % of their working time representing an average of 264.48 working hours missed per year. The total cost of absenteeism was EUR 1003 per person/year in adult employees, and EUR 2711 per person/year in children's parents. Relative presenteeism accounted to 56 % in adult patients and 80 % for paediatric patients' parents (Table 4, Table 5), meaning that, due to LHON, adult patients had reduced performance and quality of work by about 44 %, while paediatric patients' parents by about 20 %. The productivity loss as a consequence of LHON due to combined relative absenteeism and relative presenteeism was estimated to EUR 9840 per an adult patient/year, respectively, EUR 6298 per a parent/year. Societal productivity loss comprising those on disability pension, unemployed, or on a part time job was estimated to be EUR 11,611 per a patient/year. The disability pension and unemployed support accounted for EUR 5016 per person/year.

The correlation between the duration of LHON from the onset and the values of relative absenteeism and presenteeism was analysed using the Pearson correlation coefficient. No statistically significant correlation was found (see Supplement).

3.1.3. Non-medical direct costs

Out of the adult patients, 52.4 % required assistance in performing usual activities of daily living (ADLs), predominantly provided by their relatives (54.5 %). Family members and non-relatives at paid service together took care 1.83 (SD 1.94) hours per day in average. The mean cost of informal care was estimated at EUR 4502 (SD EUR 4772; n = 6) per person/year.

Most patients (62.9 %) have to travel more than 2 h to visit their specialist/ophthalmologist and one trip (round trip) to the specialist costs an average of EUR 41 per person. The mean cost of visual aids and/or adaptation and modification of domestic environment was estimated at EUR 1153 per person/year. Only four patients reported a need of rehabilitations with the average cost of EUR 1099 per patient. Most patients (n = 17) took supplements/supportive treatment, and its average cost was estimated at EUR 497 per person/year.

3.1.4. Quality of life

The mean VFQ-25 score for adult patients with LHON was 43.47 (SD 15.86; Min 23.89, Max 81.04). The near vision sub-scale had the score (28.92; SD 21.27; range Min 0, Max 75), which was the lowest among other vision targeted sub-scale scores (Table 6). Regarding paediatric eye questionnaire (PedEyeQ), four domains were scored independently. The mean score of the functional vision domain was 37.5 (SD 19.36; Min 10, Max 55), the social domain 61.25 (SD 13.15; Min 50, Max 75), and the frustration/worry domain 52.5 (SD 19.36; Min 30, Max 75). As regards the parents, the mean score of the impact on parent and family domain was 62.5 (SD 23.98; Min 40, Max 90; see Table 7).

Linear correlation was used to investigate whether the duration of LHON affects QoL. However, no statistically significant correlation was found using the Pearson correlation coefficient between the duration of LHON from onset and QoL in both adults and children, as determined by the scores of VFQ-25 and PedEyeQ (see Supplement).

The patients were also divided into groups based on the duration of LHON from onset. All adult patients had chronic LHON (>1 year from onset) and were categorized into three groups: 2–5 years (N = 4), 6–9 years (N = 8), and more than 10 years (N = 5) from the onset of LHON. The scores between these groups were compared using unpaired t-tests, but no significant differences were found. In

Table 2
Demographics.

	Adults	Children
No of individuals	21	6
Sex, n (%)		
Male	20 (95 %)	6 (100 %)
Female	1 (5 %)	0 (0 %)
Age, Years		
Mean (SD)	36.1 (13.1)	13.8 (1.83)
Range	18–70	11–16
Duration of LHON from onset, Years		
Mean (SD)	8.4 (6.0)[a]	3.3 (2.7)
Range	2–28	0.6–7
Severity of visual impairment, n (%)		
Some useful peripheral vision	7 (33.3 %)	2 (33.3 %)
Good peripheral vision	4 (19 %)	1 (16.7 %)
Light perception only (or shadows only)	2 (9.5 %)	0 (0 %)
I still have good overall vision	1 (4.8 %)	0 (0 %)
Good central vision	1 (4.8 %)	0 (0 %)
Moderate peripheral vision loss	1 (4.8 %)	2 (33.3 %)
Some useful central vision	1 (4.8 %)	1 (16.7 %)
Other	4 (19 %)	0 (0 %)
Treatment with idebenone, n (%)	17 (80.9 %)	6 (100 %)

[a] Duration of LHON was available only from 18 adult patients.

Table 3
Frequency of employment status of adult patients and paediatric patients' parents.

Employment status	Adult patients	Children's parents
Disability pension	38 %	9 %
Full time work	24 %	91 %
Part time work	14 %	0 %
Student	19 %	0 %
Unemployed	5 %	0 %

Table 4
Mean absenteeism and presenteeism (in %).

Adult patients	Mean	Median	Min	Max	Total costs per person/year
Relative absenteeism	6	0	−5	25	EUR 1003
Relative presenteeism	56	50	25	100	EUR 8659
Combination relative absenteeism and presenteeism	50	48	25	85	EUR 9840
Informal care (missed hours per day)	1.83h	1.5h	0	5	EUR 4502

Note: The negative value represents extra hours worked by patients.

Table 5
Mean absenteeism and presenteeism (in %).

Children's parents	Mean	Median	Min	Max	Total costs per person/year
Relative absenteeism	29 %	25	−5	60	EUR 2711
Relative presenteeism	82 %	90	60	100	EUR 3542
Combination relative absenteeism and presenteeism	68 %	57	23	120	EUR 6298

Note: The negative value represents extra hours worked by patients.

Table 6
Mean score of VFQ-25 scale.

Adult patients (Score 0 is the worst and 100 is the best)	Mean	SD	Median	Min	Max
Total VFQ25_score	43.47	15.86	38.75	23.89	81.04
General health	44.12	22.59	50.00	0.00	75.00
General vision	34.12	15.43	40.00	20.00	60.00
Ocular pain	64.71	21.76	62.50	37.50	100.00
Near activities	28.92	21.27	25.00	0.00	75.00
Distance activities	37.25	21.06	41.67	0.00	83.33
Social functioning	42.65	27.97	37.50	0.00	100.00
Mental health	50.74	24.40	50.00	0.00	93.75
Role difficulties	44.12	32.51	25.00	0.00	100.00
Dependency	52.94	27.63	50.00	8.33	100.00
Driving	87.50	5.89	87.50	83.33	91.67
Colour vision	61.76	20.00	50.00	25.00	100.00
Peripheral vision	50.00	21.65	50.00	25.00	75.00

Table 7
Mean score of PedEyeQ.

Children and their parents (Score 0 is the worst and 100 is the best)	Mean	SD	Median	Min	Max
Functional vision domain	37.50	19.36	42.50	10.00	55.00
Social domain	61.25	13.15	60.00	50.00	75.00
Frustration/worry domain	52.50	19.36	52.50	30.00	75.00
Impact on parent and family domain	62.50	23.98	60.00	40.00	90.00

the paediatric cohort, two patients were in the acute phase (≤1 year from the onset) and four patients were in the chronic phase (>1 year from the onset). The analysis showed no significant differences between these groups, which is consistent with the findings in adults (see Supplement).

4. Discussion

As far as we are aware, this is the first study describing the direct non-medical and indirect costs associated with LHON and is also the first study of the quality of life of LHON patients and their families in the Central and East European region. Czechia and Slovakia are countries with a similar socio-economic status, which allowed the cost calculations jointly for both countries; the situation regarding LHON patient management, however, is considerably different in favour of Czechia. The establishment of the Centre for Patients with Mitochondrial Optic Neuropathies, which provides multidisciplinary care and effective collaboration between Department of Ophthalmology and Department of Paediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital in Prague and subsequent education of peripheral ophthalmologists and neurologists, has made the diagnosis of LHON more efficient and significantly faster (the average time has changed from 9 months before 2015 to 2 months), allowing patients to benefit from the early initiation of idebenone therapy, which is crucial for its effect. Based on published prevalence in Denmark and North-East England [10,11], the estimated number of asymptomatic carriers is over 300 and 80–90 patients with manifested disease in the Czechia [13]. Currently, the centre records 150 genetically confirmed carriers (both symptomatic and asymptomatic) of prevalent mutations. In Slovakia, there is no specific centre for the treatment of LHON or inherited retinal diseases (IRDs). Paediatric patients are centralized in the Centre for Rare Diseases in the Children's University Hospital in Bratislava. The number of adult patients is unknown as they are dispensed in outpatient clinics across the country. The lengthy diagnostic process (up to 12 months), the low level of awareness among peripheral physicians, and the reimbursement of idebenone only on an exception from insurance companies (the process takes 2–3 months) represent a significant medical burden of this disease for patients in Slovakia. This could be partly solved, following the example of the Czechia, by the establishment of a complex diagnostic and therapeutic centre (not only) for LHON patients.

The recent study from the United States summarizing information on up to 400 rare diseases has shown that indirect and non-medical costs drive economic burden of rare diseases and exceed the direct medical costs [26]. Similar conclusions were reached by the authors of two cost of illness studies focused on the IRDs (including LHON) [27,28]. Our findings also highlight that patients living with LHON incur high economic costs and face a lower quality of life. Symptomatic LHON patients experience a reduced capacity to effectively participate in the workforce in comparison with the general population [28]. Compared to the absenteeism, which was reported by participants as only 6 % of the working time, the presenteeism occurs more frequently and may have a larger effect on the productivity loss. We estimated individual productivity loss due to the presenteeism at EUR 9840. Moreover, a third of patients (38 %) were on disability pension due to LHON.

The direct non-medical costs reported by the survey participants covered visual aids, modifications of domestic environment and education fees totalling up to EUR 500 per month. Because informal caregivers of adult patients did not directly participate in the questionnaire survey, the cost of informal care was calculated as direct non-medical cost using the opportunity cost approach, instead of lost productivity. The average cost of informal care for an adult patient by a family member amounted at EUR 4,502, which represents, in other words, an additional financial loss to the household resulting from LHON and constitutes a significant economic burden for patients and their families.

In general, patients with severe visual impairment diseases experience a significant impact on their quality of life, especially in terms of visual function. The impaired activities of daily living such as reading, driving, and navigating the environment can lead to social isolation, anxiety, and depression. The results of our study show that the mean VFQ-25 score for adult patients with LHON was 43.47, which is lower than that of other published IRDs [17]. The impact of the disease on patients' social life and mental health contributed to this to a significant extent, when one third of adult patients reported at least one visit to a psychologist/psychiatrist in the last twelve months. This supports the findings of Chen et al. [29] who conducted a qualitative study in France, Germany, the United Kingdom, and the United States, involving 17 LHON patients and their relatives. They concluded that "addressing the psychosocial impact of LHON and helping patients and their relatives adapt and cope with vision loss are vital".

The age at disease onset is one of the factors affecting quality of life. Previously it was shown that the vision loss associated with LHON has significant negative psychological and psychosocial effects predominantly in adolescents, young adults, and middle-aged adults [20]. In our paediatric population (mean age 13.8), quality of life was most affected in the vision functioning domain, together with a significant reduction in other domains related to frustration/worries or social interactions. Up to 67 % paediatric patients reported a need to consult a psychologist/psychiatrist over the last year.

However, Ciu et al. [18] showed that patients, especially younger ones, can spontaneously improve their vision-related QoL, which may be related to better acceptance of the disease and coping over time. Our study found no statistically significant correlation or differences between the duration of LHON from onset and quality of life in both children and adults.

The PedEyeQ questionnaire also allows to assess the impact of the eye disease on the paediatric patient's parent and close family. The presented *Impact on parent and family domain* mean score of 62.5 clearly demonstrated the negative spill over impact of the LHON in paediatric patients on their family well-being.

4.1. Limitations of the study

The study has some significant limitations. The main is the size of the sample. As LHON is a rare disease with a low prevalence (for Europe, a rough estimate of symptomatic patients is 20 cases per one million inhabitants), any study is valuable, and the sample size was similar as in some other studies. A meta-analysis combining the existing results is a challenge for future research. Our research is based on a patient self-reported survey that was available only online. Thus, it may have been potentially susceptible to data bias. Firstly, it was a convenient sample (although all patients from the register were addressed) of those who agreed to answer. Secondly,

the online form of the questionnaire may have affected the analysis through potential non-participation of patients from low-income households. These households generally experience digital poverty, which may be exacerbated by the inability to obtain the necessary low vision aids for the patient(s) due to financial constraints.

5. Conclusion

The results of this study clearly show that patients with LHON and their families face to an extensive socioeconomic burden related to this rare disease. Early, timely and appropriate access to diagnosis, treatment, and reimbursement decisions, but also to psychological counselling and services (preferably directly in the treatment centre) may help the patients and their relatives adapt and cope with the challenging aspects of vision loss and life with the disease.

Institutional review board statement

The study was approved by the Ethics Committee of the National Institute of Children's Diseases, Slovakia under the number EK/5/2022, and by the Ethics Committee of the General University Hospital in Prague under the number 102/22S.

Informed consent statement

All participants signed a written informed consent.

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Data availability statement

Data from the study is outside of CHIESI's data sharing policy and the authors do not have permission to share data.

CRediT authorship contribution statement

Beáta Bušányová: Writing – review & editing, Investigation. **Marie Vajter:** Writing – review & editing, Investigation, Funding acquisition. **Silvie Kelifová:** Writing – review & editing, Investigation. **Petra Lišková:** Writing – review & editing, Supervision. **Hedviga Miková:** Writing – review & editing, Investigation. **Katarína Breciková:** Writing – original draft, Visualization, Resources, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Ján Žigmond:** Software, Formal analysis. **Vladimír Rogalewicz:** Writing – review & editing, Visualization, Supervision. **Aleš Tichopád:** Writing – review & editing. **Martin Višňanský:** Writing – review & editing, Methodology. **Ivana Šarkanová:** Writing – review & editing, Resources, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32296.

References

[1] P.Y.W. Man, D.M. Turnbull, P.F. Chinnery, Leber hereditary optic neuropathy, J. Med. Genet. 39 (3) (Mar 2002) 162–169, https://doi.org/10.1136/jmg.39.3.162.
[2] D. Milea, P. Amati-Bonneau, P. Reynier, D. Bonneau, [2–4] Current Opinion in Neurology 23 (1) (Feb 2010) 24–28, https://doi.org/10.1097/WCO.0b013e3283347b27.
[3] P. Yu-Wai-Man, P.G. Griffiths, G. Hudson, P.F. Chinnery, Inherited mitochondrial optic neuropathies, J. Med. Genet. 46 (3) (Mar 2009) 145–158, https://doi.org/10.1136/jmg.2007.054270.
[4] D.C. Wallace, et al., MITOCHONDRIAL-DNA mutation associated with lebers hereditary optic neuropathy, Science 242 (4884) (Dec 1988) 1427–1430, https://doi.org/10.1126/science.3201231.
[5] N. Howell, I. Kubacka, S. Halvorson, B. Howell, D.A. McCullough, D. Mackey, Phylogenetic analysis of the mitochondrial genomes from leber hereditary optic neuropathy pedigrees, Genetics 140 (1) (May 1995) 285–302.

[6] R.J. Oostra, P.A. Bolhuis, F.A. Wijburg, G. Zornende, E.M. Bleekerwagemakers, Lebers hereditary optic neuropathy - correlations between mitochondrial genotype and visual outcome, J. Med. Genet. 31 (4) (Apr 1994) 280–286, https://doi.org/10.1136/jmg.31.4.280.
[7] R. Hage, C. Vignal-Clermont, Leber hereditary optic neuropathy: review of treatment and management, Front. Neurol. 12 (May 2021) 651639, https://doi.org/10.3389/fneur.2021.651639.
[8] A. Puomila, et al., Epidemiology and penetrance of Leber hereditary optic neuropathy in Finland, Eur. J. Hum. Genet. 15 (10) (Oct 2007) 1079–1089, https://doi.org/10.1038/sj.ejhg.5201828.
[9] B. Mascialino, M. Leinonen, T. Meier, Meta-analysis of the prevalence of Leber hereditary optic neuropathy mtDNA mutations in Europe, Eur. J. Ophthalmol. 22 (3) (May-Jun 2012) 461–465, https://doi.org/10.5301/ejo.5000055.
[10] T. Rosenberg, et al., Prevalence and genetics of leber hereditary optic neuropathy in the Danish population, Invest. Ophthalmol. Vis. Sci. 57 (3) (Mar 2016) 1370–1375, https://doi.org/10.1167/iovs.15-18306.
[11] P.Y.W. Man, P.G. Griffiths, D.T. Brown, N. Howell, D.M. Turnbull, P.F. Chinnery, The epidemiology of Leber hereditary optic neuropathy in the North East of England, Am. J. Hum. Genet. 72 (2) (Feb 2003) 333–339, https://doi.org/10.1086/346066.
[12] G.S. Gorman, et al., Prevalence of nuclear and mitochondrial DNA mutations related to adult mitochondrial disease, Ann. Neurol. 77 (5) (May 2015) 753–759, https://doi.org/10.1002/ana.24362.
[13] H. Kolarova, et al., Leber hereditary optic neuropathy, Ces. Slov. Neurol. Neurochir. 80 (5) (2017) 534–544, https://doi.org/10.14735/amcsnn2017534.
[14] C.B. Catarino, et al., Real-world clinical experience with idebenone in the treatment of leber hereditary optic neuropathy, J. Neuro Ophthalmol. 40 (4) (Dec 2020) 558–565, https://doi.org/10.1097/wno.0000000000001023.
[15] T. Klopstock, et al., A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy, Brain 134 (Sep 2011) 2677–2686, https://doi.org/10.1093/brain/awr170.
[16] V. Carelli, et al., International consensus statement on the clinical and therapeutic management of leber hereditary optic neuropathy, J. Neuro Ophthalmol. 37 (4) (Dec 2017) 371–381, https://doi.org/10.1097/wno.0000000000000570.
[17] M.A. Kirkman, et al., Quality of life in patients with leber hereditary optic neuropathy, Invest. Ophthalmol. Vis. Sci. 50 (7) (Jul 2009) 3112–3115, https://doi.org/10.1167/iovs.08-3166.
[18] S.L. Cui, H.Q. Jiang, J.T. Peng, J.W. Wang, X.J. Zhang, Evaluation of vision-related quality of life in Chinese patients with leber hereditary optic neuropathy and the G11778A mutation, J. Neuro Ophthalmol. 39 (1) (Mar 2019) 56–59, https://doi.org/10.1097/wno.0000000000000644.
[19] J. Ferguson, G. de Abreu, What is the lived experience for people with Leber Hereditary Optic Neuropathy? Br. J. Vis. Impair. 34 (2) (May 2016) 111–122, https://doi.org/10.1177/0264619615616260.
[20] G.A. Garcia, et al., Profound vision loss impairs psychological well-being in young and middle-aged individuals, Clin. Ophthalmol. 11 (2017) 417–427, https://doi.org/10.2147/opth.s113414.
[21] R.C. Kessler, et al., The world health organization health and work performance questionnaire (HPQ), J. Occup. Environ. Med. 45 (2) (Feb 2003) 156–174, https://doi.org/10.1097/01.jom.0000052967.43131.51.
[22] C.M. Mangione, P.P. Lee, P.R. Gutierrez, K. Spritzer, S. Berry, R.D. Hays, Development of the 25-item national eye Institute visual function questionnaire, Arch. Ophthalmol. 119 (7) (Jul 2001) 1050–1058, https://doi.org/10.1001/archopht.119.7.1050.
[23] S.R. Hatt, et al., Development of pediatric eye questionnaires for children with eye conditions, Am. J. Ophthalmol. 200 (Apr 2019) 201–217, https://doi.org/10.1016/j.ajo.2019.01.001.
[24] E. Vodrazkova, S. Sefcikova, M. Helbich, Psychometric validation of visual function questionnaire (NEI VQF-25) under local conditions in Slovakia, E.U, Ceská a Slov. Oftalmol. : casopis Ceske oftalmologicke spolecnosti a Slovenske oftalmologicke spolecnosti 68 (3) (2012 2012) 102–105, 107-105.
[25] D.A. Leske, et al., Assessing eye-related quality of life and functional vision in children with visual impairment, using the new PedsEyeQ pediatric eye questionnaires, J. Am. Assoc. Pediatr. Ophthalmol. Strabismus 23 (4) (2019/08/01/2019) e41, https://doi.org/10.1016/j.jaapos.2019.08.147.
[26] G. Yang, I. Cintina, A. Pariser, E. Oehrlein, J. Sullivan, A. Kennedy, The national economic burden of rare disease in the United States in 2019, Orphanet J. Rare Dis. 17 (1) (Apr 2022) 163, https://doi.org/10.1186/s13023-022-02299-5.
[27] O. Galvin, et al., The impact of inherited retinal diseases in the republic of Ireland (ROI) and the United Kingdom (UK) from a cost-of-illness perspective, Clin. Ophthalmol. 14 (2020) 707–719, https://doi.org/10.2147/opth.s241928.
[28] J. Gong, et al., The impact of inherited retinal diseases in the United States of America (US) and Canada from a cost-of-illness perspective, Clin. Ophthalmol. 15 (2021) 2855–2866, https://doi.org/10.2147/opth.s313719.
[29] B.S. Chen, E. Holzinger, M. Taiel, P. Yu-Wai-Man, The impact of leber hereditary optic neuropathy on the quality of life of patients and their relatives: a qualitative study, J. Neuro Ophthalmol. 42 (3) (Sep 2022) 316–322, https://doi.org/10.1097/wno.0000000000001564.