Summary
Leber’s hereditary optic neuropathy (LHON) is a rare disorder that mainly presents in males in their young age. The majority of cases are caused by three primary maternally inherited mtDNA point mutations (m.3460G > A, m.11778G > A, and m.14484T > C) that affect subunits 4, 6, and 1 of NADH dehydrogenase, respectively. It impairs glutamate transport and increases reactive oxygen species production, leading to apoptosis of ganglion cells, atrophy and demyelination of optic nerves, chiasm and pathways. This leads to visual disturbances such as painless, subacute or acute loss of central vision, initially in one eye and after few weeks or months in the other eye. The clinical expression of LHON depends on the primary mutations. M.3460G > A and m.11778G > A have been reported to have severe visual impairment and poor visual recovery, while m.14484T > C has the best long-term visual outcome with a better partial visual recovery rate. In some cases, it is observed that LHON may also manifest in extraocular symptoms, such as cardiac, skeletal, or neurological abnormalities. Currently, idebenone is the only approved drug for the treatment of visual impairment in patients with LHON. The optimal target population, timing, dose, and frequency of administration of idebenone remain controversial. Therefore, this article discusses the aetiology and pathogenesis, clinical expression according to mtDNA mutation, treatment, and response to treatment according to mtDNA mutation.
Research material and methods

A review of scientific articles was made on LHON etiology and pathogenesis, clinical expression according to mtDNR mutation, treatment, and response to treatment according to mtDNA mutation. The search was conducted in PubMed and Springer databases. Keywords and their combinations were used to identify the proper articles: Leber hereditary optic neuropathy, mutations, etiology and pathogenesis, clinical manifestation, treatment. Only studies published in English were included.

Research results

Etiology and pathogenesis. LHON was the first disease linked to mitochondrial DNA point mutations [3]. The vast majority of cases are due to 3 mutations in mitochondrial complex I subunit coding genes in mtDNA. The primary, most common point mutations are m.11778G > A, m.14484T > C and m.3460G > A. These affect subunits 4, 6 and 1 of NADH dehydrogenase, respectively, and are referred to as ND4, ND6 and ND1 mutations [4]. Because they cause defects in multiple NADH-ubiquinone oxidoreductase chains, they are thought to impair glutamate transport and increase the production of reactive oxygen species. This leads to apoptosis of ganglion cells, atrophy and demyelination of optic nerves, chiasm and visual pathways [5]. In addition to abnormalities of mitochondrial respiratory activity, other factors may play a role in mitochondrial dysfunction [6]. The phenotypic expression of LHON can be influenced by environmental factors and nuclear genes controlling mitochondrial gene expression [3].

Environmental factors, including alcohol consumption and tobacco smoking, have been identified as contributors to vision loss in people with a genetic predisposition to LHON. Studies have shown that heavy smokers are more likely to experience vision loss than light smokers. Cigarette smoking can lead to impaired complex I and cytochrome c oxidase activity and increased production of ROS, suggesting a strong causal link between smoking and increased risk of vision loss in LHON [7,8]. Heavy alcohol consumption also adversely affects disease development in LHON mutation carriers. However, this association is less significant than that of smoking. Other environmental factors, such as drugs with mitochondrial toxicity, head trauma, industrial toxins, and nutritional deficiencies, such as low vitamin B12 levels, can also trigger vision loss in LHON carriers [7]. Psychological stress may also promote LHON pathogenesis [9]. The apparent differences between the sexes require further explanation, as hormonal factors have been shown to be potential disease modifiers. Estrogen derivatives have been found to decrease ROS levels and improve survival by upregulating mitochondrial biogenesis [8]. In addition, an X-linked susceptibility factor is thought to alter disease risk. Possession of two X chromosomes protects female individuals from gene variants on the X chromosome that increase susceptibility to pathogenesis [9]. According to the literature, the maximum age of onset is reported between 15 and 35 years [10]. However, a young age of onset (12 years or less) offers the best chance of a good visual outcome [11]. Previous studies have shown that children with disease onset at age 12 years or younger have significantly better visual outcomes compared with adult LHON patients [10]. However, a final visual acuity of more than 20/200 is rare [11].

Clinical manifestation according to mIDNR mutation

m.11778G>A (MT-ND4). One of the most common genes in which most LHON mutations occur is the MT-ND4 gene, also known as mitochondrially encoded NADH:ubiquinone oxidoreductase core subunit 4 (MT-ND4) [12]. Mutation in this gene affects mitochondrial cardiolipins, which may play a role in signalling events promoting mitophagy and apoptosis [12,13]. Primary mitochondrial diseases such as LHON are highly sensitive to mitochondrial dysfunction and can severely affect cell growth and synthesis of important biological molecules. There are numerous mitochondria in retinal neurons, particularly in the pre- and intralaminar regions of the optic nerve head. Therefore, patients with LHON tend to have selective loss of RGC axons in the region of the optic disc [9]. Approximately 70-90% of people affected by LHON worldwide have a point mutation m.11778G > A in the MT-ND4 gene [14]. Although there are many other mutations in the ND4 gene, such as m.11204T > C, m.11430C > G, m.11213T > G, m.11447G > A, and m.10934G > A, the frequencies of these mutations are relatively low [1]. Studies have shown that the m.11778G > A mutation in ND4 represents the most severe clinical form of LOHN, as it causes the most severe LHON-related visual loss. It is associated with the lowest partial visual recovery rate of 4% and poor overall outcome [7,9,11]. However, the clinical manifestation of m.11778G > A and other primary mutations vary in different populations and different pedigrees [9]. Many studies suggest that the primary mutations alone are not sufficient to cause the observed clinical phenotypes [15,16]. Other factors, such as mtDNA haplogroup background, core genetic background, and environmental factors may promote modulation of phenotypic expression and disease severity [15]. The penetrance of LHON is hypothesized to be affected by heteroplasmy. A certain amount of wild-type mtDNA can compensate for the mutant mtDNA in a cell or tissue until it crosses the critical threshold and is responsible for the expression of LHON. The critical threshold is lower in
metabolically active tissues, such as the axons of the RGCs that form the optic nerve. Most LHON patients, 80-90%, carry homoplasmic mutations. The incomplete penetrance of LHON cannot be attributed to heteroplasm alone [7]. Many other mtDNA sequence variants may play a synergistic role with the primary mutations in modulating the clinical expression of LHON. In the European population, the m.11778G > A mutation is strongly associated with the J haplogroup. Haplogroups J1 and J2 increase the risk of vision loss in LHON patients with m.11778G > A, while haplogroup H plays a protective role [17]. Further studies have shown that haplogroup K and its characteristic variants have a negative impact on the m.11778G > A mutation and may modulate LHON phenotype, expression and/or penetrance in male Polish patients. This can occur through subtle conformational changes that alter assembly kinetics and stability of respiratory chain complexes [14]. In the Chinese population, carriers of the m.11778G > A mutation had an increased risk of vision loss when inherited with haplogroup M7b1’2 and a decreased risk with haplogroup M8a [7]. However, it is not clear whether these results are limited to a handful of examples or whether it is a more general phenomenon [18].

**Clinical manifestation according to mtDNA mutation**

**m.3460G>A (MT-ND1).** A m.3460G > A is a point mutation in the mitochondrially encoded NADH-ubiquinone oxidoreductase core subunit 1 (MT-ND1). MT-ND1 is responsible for the formation of NADH dehydrogenase 1, a protein of complex-I (CI). This mutation reduces the activity of CI by up to 60-80% [12]. An m.3460G > A is the rarest of all three primary mutations, occurring in only 13% of all LHON patients [19]. Although it is the rarest mutation, it is known to cause severe visual impairment and one of the worst visual recovery [2,19]. In addition to this primary mutation, several DNA sequence variants have also been reported to affect the clinical manifestation of LHON. In a large meta-analysis of Caucasian LHON pedigrees, carriers of m.3460G > A were found to have an increased risk of vision loss on a haplogroup K background. Other studies have shown that haplogroup J has the same effect as haplogroup K in terms of vision loss in carriers of m.14484T > C [1]. In the absence of ocular symptoms, LHON may also have extraocular manifestations. Individuals who carry the point mutation m.3460G > A have a risk of experiencing cardiac disorders such as hypertrophic cardiomyopathy, hypertrophy of the left ventricle, or ECG abnormalities [20]. In isolated cases, an m.3460G > A mutation can manifest as mental retardation, migraine and epilepsy [21]. Multiple sclerosis-like disorders are also associated with this mtDNA point mutation, as with other primary mtDNA mutations, but with a tendency to manifest in females [2]. Studies show that extraocular symptoms can be associated with secondary mutations. For example, an m.3460G > A homoplasmic mutation, along with haplogroup J and several secondary mutations was shown to be associated with rapid bilateral progression of ocular symptoms in a variety of valvular heart diseases. In a family with a heteroplasmic mother and homoplasmic offspring, an m.3460G > A with haplogroup U and other secondary mutations occurred as a rapid bilateral progression of ocular symptoms accompanied by dizziness, gait instability, and hand holding tremor. However, the association between secondary mutations and extraocular manifestations remains controversial [22].

**Clinical manifestation according to mtDNA mutation**

**m.14484T>C (MT-ND6).** An m.14484T > C mutation in the mitochondrially encoded NADH-ubiquinone oxidoreductase core subunit 6 (MT-ND6) accounts for the remaining 10-25% of cases of LHON and is a predominant variant in individuals of French-Canadian ancestry (90%). The clinical manifestation of this mutation is similar to other primary mutations, but it has a relatively benign illness course. With a partial vision recovery rate of 37-58%, patients with the m.14484T > C mutation have the greatest long-term visual prognosis [1,2]. In isolated cases, a 14484 mutation can manifest in retinal thinning, cone rod dysfunction, and loss of vision in one eye [23]. A study from China showed an LHON patient with a 14484T > C mutation who had bilaterally re-
duced visual acuity and external ophtalmoplegia. In another case, the mutation presented as central serous retinopathy, which included optic nerve atrophy and impaired visual acuity [24]. When the mutation occurs with haplogroup U and other additional mutations, typical ocular symptoms may be accompanied by central demyelination, cortical ischemic lesions, and valvular disease [22]. However, it is possible that these findings are limited to a few cases [18].

An association between all three primary pathogenic mtDNA variants causing LHON (m.3460G>A, m.11778G>A and m.14484T>C) and multiple sclerosis-mimicking LHON has been established, particularly in women (Table 1,2) [25].

**Treatment**

There are 7 unapproved treatments for LHON. Several dietary supplements such as vitamins B2, B3, B12, C, E, and folic acid can be recommended to LHON patients to improve mitochondrial respiration and scavenge free radicals to lower reactive oxygen species and harmful acyl-coenzyme A molecules. Unfortunately, the benefit of dietary supplements for LHON patients is still limited and inconsistent [26]. Patients are also advised to stop smoking and reduce alcohol consumption, as these neurotoxins can increase oxidative stress [4]. Brimonidine, a topical A2 agonist, has neuroprotective benefits in a several animal models. However, in a clinical trial for prophylaxis of second eye involvement in LHON subjects, brimonidine failed. Another treatment option is cyclosporine A, an immunosupressant that is effective for preventing apoptosis in damage-induced cell death. Cyclosporin A has been proposed to be beneficial in the early stages of LHON by showing the diseases natural course, however, one research found that cyclosporin A did not stop second eye involvement[27,28]. Phytoestrogens target estrogen receptor b and increase cell survival by reducing apoptosis, promoting mitochondrial biogenesis, and significantly lowering ROS levels in LHON cells. In those who carry the mutation but unaffected, the medication should stop visual loss. However, only in vitro procedures were used in the study[29]. Gene therapy involves administering a gene intravitreal, subretinal or suprachoroidal to replace a damage gene with a normal wild-type gene. It aids in stopping RGC degeneration and restoring complex I activity [30]. Gene therapy is a viable, secure, and efficient treatment option that has shown promise in long-term studies. However, gene therapy mainly focuses on the m.11778G > A mutation and cannot be used for other primary mutations [31].

The Stem Cell Ophthalmology Treatment Study uses bone marrow-derived autologous stem cells to treat diseases of optic nerve. Their research has demonstrated that stem cells can improve visual acuity and visual field without experiencing any significant side effects. However, further research is needed [32]. Idebenone is the only medication licensed to treat LHON. It is an antioxidant that can avoid complex I in the mitochondrial electron transport chain and transfer electrons directly to complex III, resuming the cell’s ability to produce energy [33]. Idebenone enhances and prevents visual function regression. All three of the main mutations are treated with this method [26].

**Response to treatment depending on mtDNA mutation.** Currently, age at onset of vision loss and mitochondrial genotype rank as the two most significant predictive factors for vision. Variable rates of vision recovery range from 4% to 25% for the m.11778G > A mutation to 22% to 25% for the m.3460G > A mutation and 37% to 1% for the m.14484T > C mutation. Many studies reported that vision improved in patients with idebenone m.11778G > A, which was beyond the expected natural history of the disease [4,30]. The m.14484T > C mutation likewise responded well to treatment with Idebenone [4,26]. This mutation is known to have the highest rate of spontaneous cure. After m.14484T > C was eliminated from the research, patients who had recently started losing their vision showed the best response to treatment [30].

**Conclusions**

1. LHON is a blinding, maternally inherited disease with variable penetrance. Three primary mitochondrial DNA mutations (m.11778G > A, m.3460G > A, 14484T > C) are necessary but not sufficient to develop optic neuropathy. MtDNA haplogroup background, secondary mutations, core genetic background, and environmental factors may play an important role in modulating the phenotypic expression and severity of LHON.

2. The m.11778G > A mutation is the most common and results in the most severe LHON-related visual loss with the lowest partial recovery rate and poor overall outcomes.

3. In contrast, the m.14484T > C mutation has a more benign disease course and the best long-term visual outcomes with a good partial visual recovery rate.

4. An m.3460G > A is the most uncommon form which causes severe visual impairment and one of the worst visual recovery rates. Idebenone remains the cornerstone treatment and the only approved drug for LHON.

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PAVELDIMOS LĖBERIO OPTINĖS NEUROPATIJOS MUTACIJOS IR JŲ RYŠYS SU KLINIKINĖMS IŠRAIŠKOMIS

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Raktažodžiai: paveldima Lėberio optinė neuropatija, mutacijos, etiologija ir patogenezė, klinikinės išraiškos, gydymas.

Santrauka

Paveldima Lėberio optinė neuropatija (PLON) yra reta liga, kurią dažniausiai serga jauni vyrai. Didžiąją dalį PLON ligos atvejų sukélia viena iš trijų mtDNR taškinių mutacijų – m.33460G>A, m.11778G>A ar m.14484T>C, kurios atitinkamai paveikia 4, 6 ar 1 NADH dehidrogenazės subvienetus. Taip sutrikdomas glutamato transportavimas ir padidintama reaktyviųjų deguonies radikalų gamyba. Įvyksta ganglinių ląstelių apoptozė, atrofuojasi ir demielinzuojasi regos nervai, chiazma ir laidai. Visa tai pasireiškia neskausmingu, ūmiu ar poūmiu centrinio regėjimo praradimu. Požymiai pirmiausia pasireiškia vienoje akyje, o po kelių savaičių ar mėnesių ir kitoje. Klinikinė PLON raiška priklauso nuo pirminių mtDNR mutacijų. M.3460G>A ir m.11778G>A sukelia sunkius regėjimo sutrikimus ir prastą atsigavimą, o m.14484T>C turi geriausias ilgalaikes regėjimo baigtis bei geriausią regos atsigavimo rodiklį. Pastebėta, kad PLON gali pasireikšti ir ekstraokuliniais simptomais, tokiais kaip širdies, skeleto ar neurologiniai sutrikimai. Šiuo metu vienintelis patvirtintas vaistas PLON gydyti yra ibedenonas, stabdantis regos funkcijos blogėjimą ir ją atsaką į gydymą, tačiau ne visada. Kiti gydymo būdai yra ieškoti priežiūrių, kai PLON gali pasireikšti ir ekstraokuliniais simptomais. Adresas susirašinti: steniulyte@gmail.com

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