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Review of literature on Leber hereditary optic neuropathy  
(LHON)  

Dziedziczna neuropatia nerwów wzrokowych Lebera – przegląd piśmiennictwa  

Key words: Leber’s Disease, Leber’s Hereditary Optic Neuropathy, mitochondrial cytopathies, visual impairment, quality of life  

Słowa kluczowe: Choroba Lebera, Dziedziczna Neuropatia Nerwów Wzrokowych Lebera, cytopatie mitochondrialne, zaburzenia widzenia, jakość życia  

INTRODUCTION  

Leber hereditary optic neuropathy (LHON) is the most common inherited optic neuropathies causing bilateral central vision loss. LHON is one of mitochondrial diseases, which are clinically heterogeneous group of disorders that arise as a result of dysfunction of the mitochondrial respiratory chain. Vision loss from LHON is outcome of selective degeneration of retinal ganglion cells layer and optic nerve axons, which are highly sensitive to mitochondrial dysfunction and metabolic insult [29]. LHON is a maternally transmitted disorder due to a mutation of mitochondrial DNA (mtDNA). Approximately 95% of cases are the result of one of the three pathogenic mtDNA point mutations: m.3460A>G, m.11778A>G and m.14484T>C. These mutations affect genes which encode different complex I subunits of the mitochondrial respiratory chain [31, 15].  

Since it was discovered, LHON has been recognized as one of the most common mitochondrial diseases with a prevalence of 1 in 31 000 in the North East of England [16]; other epidemiological studies report a prevalence of 1 in 39 000 in the Netherlands and 1 in 50 000 in Finland [27]. Symptom onset typically occurs in the second and third decades of life. LHON carriers rarely lose vision after the age of 50 years. Males are four to five times more likely than females to be affected [20,8]. Most LHON patients are aware of a family member (maternal relatives) with LHON-compatible vision loss, although 40% deny a known family history [15].
INHERITANCE

Interestingly, many individuals carrying a pathologic mutation are asymptomatic. The presence of a pathogenic mtDNA LHON-causing mutation is necessary but not sufficient for a development of LHON. Transmission of a mitochondrial genom occurs from a mother to her progeny. There is no paternal contribution, because mitochondria present in sperm are proteolytically destroyed by the zygote. Therefore, LHON results when a mother carrying a mtDNA pathogenic variant transmits it to her children, while fathers cannot transmit a mutation to any his offspring. Both male and female offspring can inherit a mutation, however approximately 50% of males and only 10% of females experience vision loss. It cannot be explained only by principles of mitochondrial inheritance [4]. These incomplete penetrance and predilection for males to develop the optic neuropathy imply that additional genetic and environmental factors must modulate a phenotypic expression of LHON. A lot of factors have been proposed to contribute to clinical conversion from an asymptomatic to a symptomatic stage, which include environmental factors (alcohol, smoking, nutritional deprivation, acute illness, psychological stress, industrial toxins, drugs that have mitochondrial toxicity such as antiretrovirals and ethambutol), hormonal factors (testosterone, low estrogen), mitochondrial genetic factors (heteroplasmy, mtDNA haplogroups) and nuclear genetic factors (recessive X linked susceptibility gene, other nuclear modifier genes) [12, 13, 24, 32].

CLINICAL MANIFESTATION

LHON carriers remain asymptomatic until they experience bilateral, simultaneous or sequential optic neuropathy. The vast majority of cases present painless, acute or subacute central visual loss in one eye. Weeks to months later, the second eye becomes involved, with a median delay of 6-8 weeks. Within one year, 97% of those affected have involvement of the second eye. Approximately 25% cases have bilateral simultaneous vision loss. Patient with unilateral optic neuropathy, which lasts longer than one year is highly unlikely to suffer from LHON-related vision loss. Visual acuity reaches a nadir 4–6 weeks after disease onset and it is severely reduced to 20/200 or worse. Other clinical features include early impairment of colour perception, papillary light reflexes remain intact and patients usually report no pain on eye movements [9, 24].

DIAGNOSIS

The diagnosis is based on ophthalmologic findings. Dilated fundus examination reveals characteristic optic disc and vascular changes in the acute phase: vascular tortuosity of the central retinal vessels, swelling of the retinal nerve fibre layer (RNFL) and a circumpapillary telangiectatic microangiopathy. However about 20% of LHON cases, the optic disc looks completely normal in the acute stage of vision loss[9, 24]. Fundus changes seen in LHON can be further characterized and quantified through optical coherence tomography – in the acute phase the RNFL thickens first in the temporal and inferior quadrants, then the superior and nasal quadrants [2]
On fluorescein angiography there is no leakage of dye from the optic disc, in contrast to most cases of acquired optic disc swelling where fluorescein leakage is in early feature. With the progression of the disease, usually 6 weeks after onset of vision loss, telangiectasia vessels and pseudopapilloedema of the disc disappears and optic atrophy takes place. Visual field shows the characteristic bilateral central or centrocecal scotoma [20,25]. Other ophthalmologic manifestations of LHON include dyschromatopsia and diminished contrast sensitivity. Slit lamp examination is normal. Visual evoked potentials (VEPs) and electroretinograms (ERGs) are often abnormal [5]. Magnetic resonance images of the brain and orbits are usually normal, although there are some case reports of non-enhancing high signals within the optic nerve [6,17] Genetic testing for the three most common disease point mutations is required for definitive diagnosis in a context of clinical manifestations concerning for LHON, especially in cases with atypical clinical features and no clear maternal history of blindness.

LONG TERM PROGNOSIS

The visual prognosis in LHON is poor. Within one year, more patients experience stabilization of their vision, but they often have severe bilateral vision deficits and are legally blind. Although most affected patients have permanent vision loss, some patients demonstrate a milder disease or demonstrate some degree of spontaneous recovery with decrease in the size of central scotoma or development of small islands of vision within the scotoma (fenestrations) [13,14] Major visual prognostic factors include type of pathogenic mutation, age of onset and optic disc size. The most common mutation 11778A>G is associated with the worst visual prognosis and the lowest visual recovery rate. A rarer mutation14484T>C results in a milder course and higher incidence of spontaneous partial visual recovery. Earlier age of onset (younger than 20 years) and larger optic disc are also associated with a better visual prognosis [32].

RARE SYMPTOMS WHICH MAY ACCOMPANY LHON

While a typical manifestation of LHON is vision loss, a subset of patients have other manifestations including cardiac arrhythmias, peripheral neuropathies, myopathy, dystonia or myoclonus. In some cases the optic neuropathy is complicated by prominent spastic dystonia, ataxia, juvenile onset encephalopathy and psychiatric disturbances. These phenotypes have been called “LHON plus syndromes” and have been linked to other mtDNA point mutations different from the three commonly seen in LHON [21] The coexistence of LHON and demyelinating syndrome that is radiologically and clinically identical to multiple sclerosis (MS) is known as “Harding’s syndrome” (LHON - MS). Patients demonstrate the LHON-MS syndrome are usually females carrying the 11778G>A mutation [12].
TREATMENT

There is currently no treatment available that improves the final visual outcome in LHON. At this time there are no established curative interventions and treatment is mainly supportive. Treatment of LHON is primarily focused on exploring antioxidants as possible therapeutic agents. The therapeutic benefit of a number of antioxidants has been explored in the past including coenzyme Q10, cyanocobalamin, folic acid and ascorbic acid, all of them have been disappointing without demonstrable benefit. However, recent studies have shown that two antioxidants, indebenone and α-tocotrienol-quinone (EPI-743), may improve the final visual outcome in affected patients. Gene therapy and use of stem cell to treat also have shown some promise for mitochondrial diseases[21, 32]. Patients should be counselled to optimize environmental risk factors for vision loss by avoiding smoking, heavy alcohol consumption, medications with mitochondrial toxicity and exposure to environmental toxins. Other supportive measures, particularly for the “LHON plus syndrome”, includes screening for extraocular manifestations of LHON, such as screening electrocardiogram and neurological examination.

SOME ASPECTS OF QUALITY OF LIFE IN LEBER NEUROPATHY

Little is known on the QoL of patients with Leber neuropathy. Increasing interest in the costs of medical care, necessity to assess efficacy and efficiency of treatment led to increasing interest in the quality of life in medicine. Epidemiological measures used so far, such as morbidity, prevalence or life expectancy as well as clinical measures became insufficient to assess many illnesses. This happened, because assessment of the functioning of the ill people may be influenced by many factors, not only general health state or physical state but also their emotional well-being, possibility of participation in family and social life. Thus, quality of life was introduced to medical sciences for the assessment of the consequences of many disorders. Presently it is known that quality of life and health status are different constructs. Quality of life is presently a vital and used together with clinical and functional assessment outcome measure, which allows to assess efficacy of the therapy, and is commonly used while introducing new therapeutic methods.

Since 1948, when the World Health Organization defined health as being not only the absence of disease and infirmity but also the presence of physical, mental and social well-being, quality of life has become steadily more important both in health care practice and in research (WHO Constitution 1952). Presently, quality of life (QoL) has firmly established position as an important endpoint in medical care. This is of particular significance in chronic disorders such as neurodegenerative disorders of central nervous system.

QOL IN LEBER’S NEUROPATHY

The was only one study assessing qol of subjects with LHON [14]. The study involved 402 subjects -196 affected and 206 unaffected, and confirmed significantly reduced QoL. LHON has a severe negative impact on quality of life and has the
worse Visual Function Index (VF-14) score when compared with other ophthalmic disorders. However, LHON patients can be reassured that their level of visual impairment is less likely to progress in time and that probably also affects their QoL assessment.

Some tools were designed both to objectively assess visual impairment and vision-dependent quality of life of patients with optic nerve disorders. The visual function index questionnaire appears to be a useful tool for assessing visual impairment in the course of LHON and measuring treatment outcome [14] VF-14 score clearly indicates the considerable visual morbidity associated with this disorder [1]. To enable measurement of QoL in patients with vision impairment, researchers designed VIS QoL - a vision-related utility instrument for the health economic evaluation of eye care and rehabilitation programs. VisQoL assessment was based on the assumption that impaired utility depends most of all on the effects of a health condition that allows patient to achieve a productive and fulfilling life in their social context [18].

The VisQoL disaggregates vision into six items. Utilities were estimated for item worst responses (the worst level for each item, with all other items at their best level) and VisQoL all-worst responses (all items at their worst level) using the time trade-off procedure [23]. Time trade-off questions require people to imagine living a fixed number of years with a particular health condition and then indicate how many of those years of life they would be willing to trade to have perfect health. In cases, where patients indicated their health state to be “worse than death” negative utilities were estimated. Time trade-off questions were used to minimized the “focusing effect,” which occurs if survey respondents seem not to notice the fact that all other aspects of health are at their best when answering questions [28, 30]. During the assessment some steps need to be taken to reduce the likelihood that the judgment of the entire health state will be affected by the single dimension (in this case – visual impairment).

Another aspect that may influence LHON patients’ wellbeing is family planning and contraception. Especially women with a family history of Leber’s disease should search for advice in this area. However, the genetic counseling in LHON is extremely difficult for two reasons - usually we are not able to detect the persons at risk for optic atrophy, also the amount of mutant mtDNA transmitted by heteroplasmic females cannot be predicted [11]. Not all of the individuals with 100% of mutant mtDNA develop visual symptoms. According to genealogical data, approximately 50–60% of men at risk for LHON experience significant visual loss, while the occurrence rate in affected women ranges from 8% to 32% [19].

CONCLUSIONS

Although half of patients, who carry Leber’s mitochondrial mutation will eventually fulfill the legal requirement for blind registration, impaired daily routine activities were also disabled for the group with visual acuities below this threshold. It is worth noticing, that those should also be supported by social services. It’s also worth mentioning, that most patients and their relatives benefit from informed genet-
ic counselling as far as family planning and contraception goes. Moreover we need to stress a psychological impact of vision disturbances. Some research revealed, that levels of anxiety and depression in the course of Optic Neuropathies are comparable to those seen in patients undergoing cancer treatment [10]. However psychological aspects of QoL seemed to be especially magnified in patients with Dominant Optic Atrophy (DOA), rather than in Leber’s Disease. It may result from the fact of more progressive character of visual failure in the course of DOA.

Vision impairment has a significant impact on patients’ length and QoL [29, 21]. Previous research has shown that vision disfunction is also a risk factor for sudden falls, hip fractures, depression, social isolation, and a special need for community services and what’s more it involves greater risk of admission to nursing homes [23].

That brings us to a conclusion, that patients with neurodegenerative disorders involving optic nerves represent a high-risk group that requires greater clinical input and enabled access to rehabilitative treatment to lower the additional impact of the neurological complications on the impaired visual functions. Leber’s Hereditary Optic Neuropathy may present as an ideal mitochondrial disease model for experimental intervention with its natural history of bilateral sequential visual acuity impairment lends itself to timely intervention, and its monosymptomatic localization to the optic nerve, that allows delivery of a specific, designed treatment [7].

REFERENCES


ABSTRACT

There are many primary neurological disorders leading to the significant deterioration of quality of life due to impaired vision. This is especially relevant while considering the relatively young people who initiates their adulthood. The Leber’s Hereditary Optic Neuropathy is an example of disease which is still being researched in spite of already known maternal pattern of mitochondrial DNA mutations inheritance. The reason is multifactor influence on symptomatic onset of this disease in particular mutations’ carriers, including gender, various environmental effects or another unknown genetic abnormalities.

STRESZCZENIE

Wiele spośród chorób pierwotnie neurologicznych prowadzi do znaczącego pogorszenia jakości życia w mechanizmie upośledzenia widzenia. Ma to szczególne znaczenie jeżeli dotyczy populacji ludzi względnie młodych, którzy wkraczają w dorosłe życie. Przykładem takiego schorzenia jest dziedziczna neuropatia nerwów wzrokowych Lebera, która pomimo znanego matczynego wzorca przekazywania poszczególnych mutacji w mitochondrialnym DNA jest wciąż przedmiotem wielu badań. Przyczyną tego stanu rzeczy jest mnogość potencjalnych czynników takich jak płeć, wpływ środowiska zewnętrznego lub nieznane do tej anomalia genetyczne, które warunkują objawową manifestację kliniczną schorzenia u nosicieli poszczególnych mutacji.

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