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Case report / Приказ болесника

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Leber's hereditary optic neuropathy with complete visual recovery – the first report

Леберова хередитарна оптичка неуропатија са потпуним опоравком видне оштрине – први приказ случаја

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SUMMARY

Introduction Leber's hereditary optic neuropathy (LHON) typically affects young adults with a higher prevalence in men, but can ultimately occur at any age and also in women. LHON is caused by point mutations in the mitochondrial DNA. Classically, LHON presents as a subacute unilateral loss of visual acuity, dyschromatopsia in the red-green axis and a central or centrocecal scotoma. The contralateral eye usually develops similar symptoms within 3 - 6 months of onset of the disease.

Case outline A 55-year-old male patient presented to a neurologist 20 days after the onset of vision loss. The patient was admitted as an emergency to The Clinic for the Eye Disease due to a sudden vision loss in both eyes. The best corrected visual acuity in both eyes was 4/60. The IOP on both eyes was normal. Oedema of the optic nerve head was found on the right eye and a disc with blurred borders was seen on the left eye. During hospitalisation several consultative examinations and diagnostic procedures were performed, together with blood laboratory and visual field perimetry. Genetic testing for LHON as well as antibodies to AQ4, immunoserology, virology, and lumbal puncture have been performed. VEP and ultrasound examination were performed as well.

Conclusion In our patient, the presence of a heteroplasmic mutation m.11778 G> A (MT-ND4) in mitochondrial DNA analyzed from a peripheral blood sample was shown. In the available literature, this is the first documented LHON case demonstrating complete restitution of visual acuity in both eyes with LHON.

Keywords: Leber's hereditary optic neuropathy; sudden visual loss; mitochondrial DNA mutation

САЖЕТАК

Увод Леберова хередитарна оптичка неуропатија (ЛХОН) типично погађа млађе људе са већом преваленцом код мушкараца, али може се десити у било ком животном добу и такође код жена. ЛХОН настаје због мутације у митохондријалној ДНК. Класично се ЛХОН презентује са субакутним унилатералним губитком вида, дисхроматопсијом у црвено-зеленом спектру и централним или центроцекалним скотомом. Друго око обично развија сличне симптоме за 3–6 месеци од почетка болести.

Приказ случаја Пацијент старости 55 година дошао је на преглед код неуролога 20 дана након изненадног губитка вида. Одмах је упућен као хитан случај на Клинику за очне болести због изненадног губитка вида на оба ока. Најбоље коригована видна оштрина на оба ока је износила 4/60. Интраокуларни притисак (ИОП) је био нормалан на оба ока. Едем главе оптичког нерва је био присутан на десном оку а на левом се нејасно ограничавала глава оптичког нерва. Током хоспитализације више различитих консултативних прегледа и дијагностичких процедура је урађено, заједно са лабораторијском анализом крви и компјутеризованим видним пољем. Урађена су генетска тестирања на ЛХОН као и антитела за *AQ4*, имуносерологију, вирологију и лумбалну пункцију. ВЕП и ултразвучни преглед су такође урађени.

Закључак Код нашег пацијента је пронађена хетероплазматска мутација m.11778 *G> A* (*MT-ND4*) у митохондријалној ДНК добијеном анализом узорка периферне крви. Прегледом доступне литературе, ово је први документовани ЛХОН случај који показује комплетни опоравак видне оштрине на оба ока са ЛХОН.

Кључне речи: Леберова хередитарна оптичка неуропатија; изненадни губитак вида; митохондријална ДНК мутација

INTRODUCTION

Leber's hereditary optic neuropathy (LHON) typically affects young adults with a higher prevalence in men, but can ultimately occur at any age and also in women. LHON is caused by point mutations in the mitochondrial DNA, which lead to a defect in complex I of the mitochondrial respiratory chain. This in turn causes dysfunction and later degeneration of

retinal ganglion cells, followed by ascending optic atrophy [1]. Mitochondrial deficiency of respiratory complex 1 compromises ATP production and oxidative stress management in retinal ganglion cells (RGC). The most common LHON-causing mutations are 11778G>A, 3460G>A, and 14484T>C point mutations in MT-ND4, MT-ND1, and MT-ND6 [2]. Classically, LHON presents as a subacute unilateral loss of visual acuity, dyschromatopsia in the red-green axis and a central or centrocecal scotoma. The contralateral eye usually develops similar symptoms within 3 - 6 months of onset of the disease. In 25% of cases, however, the disease begins bilaterally [1]. Most patients deteriorate to acuities worse than 20/200 (0,1). Pupillary light responses may be relatively preserved when compared with the responses in patients with optic neuropathies from other causes [3]. The classic fundus appearance triad includes: 1. hyperemia and elevation of the optic disc, with thickening of the peripapillary retina; although the disc appears swollen, it does not leak on fluorescein angiography, 2. peripapillary telangiectasia and 3. tortuosity of the medium-sized retinal arterioles. These findings can develop before vision loss begins.

The fundus can also appear entirely normal (in >40% of cases in one referral series) [4]. No treatment has been demonstrated to be effective. Corticosteroids are still one of possibilities for LHON treatment despite newer drugs such as Idebenone or gene therapy. Idebenone may increase mitochondrial energy production and may improve the outcome of LHON. Novel therapies such as estrogen and gene therapy are being explored. Controversy exists whether tobacco or excessive alcohol intake, which might stress mitochondrial function, plays an initiating role in LHON [5].

CASE REPORT

A 55-year-old male patient presented to a neurologist 20 days after the onset of vision loss. In the same time, he was treated by an otorhinolaryngologist for antibiotic-treated

sinusitis. He has been treated for arterial hypertension for several years, and wears a hearing aid. On examination, the neurological status was otherwise unremarkable. Multi-slice computer tomography (MSCT) of the endocranium revealed no pathology. Blood laboratory analyzes were performed. Complete blood count showed mild erythopenia (4.34 x1012 / l), MCV 104fL, MCH 35 pg. Biochemical analyzes showed a high value of total bilirubin 43.0 umol / L, ferritin 325 ng / ml, AST 81 U / L, ALT 145 U / L, GGT 536 U / L. Electrolyte and inflammatory factor values were within the reference range.

The patient was admitted emergently to The Clinic for the Eye Disease due to a sudden vision loss in both eyes. The best corrected visual acuity in both eyes was 4/60. The IOP was 16 mmHg on both eyes measured by applanation tonometry. Signs of dry eye were found on the anterior segment examination. The optic nerve head manifested oedema on the right eye and blurry borders on the left eye.

Computerized perimetry on the first, fourth and eighth day was performed. A centrocecal scotoma was observed in both eyes enlarging on each subsequent image. On the first day, right eye (RE) vision filed demonstrated MD -9.51 dB and -13.38 dB on the left eye (LE). On the fourth day, the MD in the RE was -9.58 dB, and in the LE -19.42 dB. On day 8, MD was -19.24 dB in the RE and -26.65 dB in the LE

During hospitalization several ancilliary examinations and diagnostic procedures were performed. X-rays of the lungs and heart, as well as paranasal sinuses did not show pathological changes. On the second day of hospitalization, MRI of the endocranium was performed, which showed supratentorially bilateral chronic microangiopathic changes in the white matter of the brain and initial periventricular ischemic leukoencephalopathy. Chronic mastoiditis was found on both sides. ANAs were not detectable.

The patient was examined by internal medicine specialist. A gastric volvulus was found and he did not receive consent for the use of pulse corticosteroid therapy at that

moment. Multi-detector row computed tomography (MDCT) of thorax was without pathological changes.

On the third day of hospitalization, a consultant neurologist introduced pulse corticosteroid therapy. Genetic testing for LHON as well as antibodies to AQ4, immunoserology, virology, and lumbal puncture have been performed. It was advised to continue with corticosteroid treatment at The Clinic for Neurology Disease. VEP testing was performed, p100 latency was prolonged on both eyes (right 136 ms, left 146 ms) were found.

Immunoelectrophoresis was performed and it identificated parallel oligoclonal IgG bands in cerebrospinal fluid and serum with identical number and intensity. The findings support systemic immune activation. A color Doppler scan of the blood vessels of the neck indicated a moderately thickened intimomedial complex with no plaques. Carotid and vertebral arteries of regular diameter and direction were found. Transcranial Color Doppler showed normal findings on the anterior and vertebrobasal blood flow. Retroorbital ultrasound revealed regular hemodynamic parameters in central retinal and ophthalmic arteries bilaterally. Clinical decision support (CDS) of the temporal artery neat was with no signs of temporal arteritis.

Detection of these mutations was performed using capillary electrophoresis on an automatic sequencer (3500 Genetic Analyzer Applied Biosystems). The results were analyzed using sequencing Analysis 5.3.1. software. In our patient, the presence of a heteroplasmic mutation m.11778 G> A (MT-ND4) in mitochondrial DNA analyzed from a peripheral blood sample was shown. This confirmed the diagnosis of Leber's hereditary optic neuropathy.

Pulse corticosteroid therapy was administered for 5 days at a dose of 1 g, after which there was a significant improvement in visual acuity. Visual acuity in both eyes was

improved to a maximum of 1.0 (200/200) and it was permanently maintained over the next two years of follow up.

Written consent for publication of the article has been obtained by the patient's family member.

DISCUSSION

In the available literature, this is the first documented LHON case demonstrating complete restitution of visual acuity in both eyes with LHON.

PCR amplification and sequencing of mitochondrial DNA regions containing mutations m.11778G> A (MT-ND4), m.14484T> C (MT-ND6), m.3460G> A (MT-ND1) which have been shown to occur in about 90% of patients with LHON.

In the Mashima et al study, the effect of Idebenone (Raxone, Santhera Pharmaceuticals, Deutschland) was monitored in patients with LHON. 25 (20.5%) of the 122 eyes had a recovery of their visual acuity to ≥ 0.2 [6].

In study Newman NJ et al, among 695 patients with LHON patients with the m.11778G>A mutation recovery of meaningful vision likely occurs in less than 20% of patients, irrespective of how recovery is defined, and ultimate visual acuities of better than 20/200 are rare [7].

The m.11778G>A LHON patients treated with gene therapy rAAV2/2-*ND4* exhibited an improvement of visual acuity over more than 4 years after vision loss to a degree not demonstrated in Natural History (NH) studies. [8].

Options for the effective treatment of hereditary optic neuropathies have been a long time coming. The successful launch of the antioxidant Idebenone for Leber's Hereditary Optic Neuropathy (LHON), followed by its introduction into clinical practice was an important step forward. Nevertheless, other options, especially for a variety of mitochondrial

optic neuropathies such as dominant optic atrophy (DOA), are needed, and a number of pharmaceutical agents, acting on different molecular pathways, are currently under development. These include gene therapy, which has reached Phase III development for LHON [9].

Our case advocated that there is no secure treatment about visual outcome in patients with LHON. Introducing pulse corticosteroid therapy as soon as possible is highly recommended in LHON patients by our experience.

Conflict of interest: None declared.

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