

LEBER HEREDITARY OPTIC NEUROPATHY

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Leber optic neuropathy is mitochondrial neurodegenerative disease manifested by progressive visual deterioration due to optic nerve atrophy. It is most frequently manifested in young people aged from 18 to 30, male patients prevailing. The disease is characterized by maternal inheritance, and the inheritance of a feature discontinues in men. In 95% cases Leber hereditary optic neuropathy is due to one of three known mitochondrial DNA mutations, its type being important in relation to the disease prognosis. The disease course has a number of succeeding stages: preclinical, acute and chronic (atrophic). The disease diagnosis is based on the characteristic clinical presentation of sequential impairment of both eyes forming central scotoma, the analysis of family history and detection of specific mutations. The present clinical observation illustrates the difficulties in Leber disease diagnosis.

Key words: optic neuropathy; Leber disease; mitochondrial disease; optic nerve atrophy.

Leber hereditary optic neuropathy or Leber optic atrophy, or Leber's disease, is a mitochondrial neurodegenerative disease, manifesting itself by a progressive reduction of vision due to optical nerve atrophy. It may develop at any age though occurs most commonly in young people from 18 to 30 years. Mutation is characterized by incomplete penetrance depending, in particular, on the type of mutation. The disease develops in 50% of male and 10% of female carriers [1, 2].

Maternal type of inheritance is characteristic for this disease, the transmission of the trait is interrupted on males. Leber hereditary optic neuropathy is caused in 95% by one of the following mutations of mitochondrial DNA: 3460G>A in gene ND1, 11778G>A in gene ND4, 14484T>C in gene ND6 [3]. In carriers of 14484>C mutation milder clinical manifestations and greater chances of spontaneous recovery are noted. The most frequent (about 50%) is mutation 11778G>A in gene ND-4 (replacement of adenine by guanine in position 11778), which encodes the structure of the enzyme NADH-ubiquinone oxidoreductase. Changing of enzyme structure leads to the impairment of interaction of ubiquinone and complex I of the respiratory chain and the increased generation of active oxygen forms. The respiratory chain defect causes energy deficiency and reticular cells, primarily ganglionic, fail to perform a high energy-consuming process of nerve impulse generation, resulting in triggering the process of apoptosis.

A number of stages is distinguished in the course of the disease: preclinical, acute, and chronic (atrophic). At the *preclinical stage* peripapillary teleangiectasias, reduction in the thickness of the nervous fibers from the

temporal side, impairment of the color vision (red–green), contrast sensitivity decrease, subnormal parameters of electroretinogram and evoked visual potentials may be revealed. At the *acute stage* gradual loss of central vision takes place. The typical manifestation of the disease is the appearance of scotoma in the field of vision of one eye. Scotoma enlarges in size, and the second eye is usually affected in 6–8 weeks. As a result, vision acuity drops in 80% of cases up to “counting fingers near the face” during 1–2 months, further in rare cases it may partly restore spontaneously again (more typical for carriers of mutation 14484>C). Objective signs are crimpiness of the reticular central vessels, edema of the nervous fiber layer, microangiopathy of the peripapillary vessels in the form of teleangiectasias. Argyll Robertson symptom — absence of pupil reaction to light, retaining at the same time their reaction to convergence and accommodation — may also be determined. *Chronic (atrophic) stage* is characterized by bilateral atrophy of the optic nerves. The accompanying neurological disorders (postural tremor, neuropathy, myopathy, dystonia, ataxia) develop in many cases, rarely becoming, however, clinically significant. In some carriers of 11778G>A mutation, mainly females, clinical signs of multiple sclerosis develop, which is associated with disseminated demyelination of the central nervous system [4].

The diagnosis of the disease must be based on the characteristic clinical picture of the successive damage of both eyes with the formation of central scotoma, analysis of family history, and revealing specific mutations.

It is necessary to carry out medico-genetic examination of the patient and his family members, to find out the

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specific features of the illness inheritance and the risk of its manifestation in the mutant gene carrier.

Difficulties in the diagnosing of this disease are illustrated below on the basis of our own clinical observations. Informed written consent was received from the patient on using his data for the scientific analysis.

A 20-year-old patient D. consulted the ophthalmologist at the Clinic of Nervous Diseases of Nizhny Novgorod Regional Clinical Hospital after N.A. Semashko, complaining of vision reduction in both eyes. In March 2012 he noticed for the first time the appearance of the “dead zone” in the central part of the field of vision of the right eye. During a month he noted the enlargement of central scotoma, the occurrence of similar changes in the other eye, pain in the eyeball. No other complaints were presented. During 8 months the patient was examined and treated in 6 medical settings of the city and the country. In all cases the diagnosis included “multiple sclerosis; retrobulbar neuritis of both eyes; atrophy of optic nerves of both eyes”. At last he addressed the Clinic of Nervous Diseases of Nizhny Novgorod Regional Clinical Hospital after N.A. Semashko for consultation. He was recommended to undergo a moleculo-genetic examination in order to exclude Leber hereditary optic neuropathy. The examination revealed mutation 11778G>A in a homoplasmic state.

A comprehensive history-taking helped to find out that his second cousin, living in another region, had been suffering from the same illness since 2006. Speaking with him over the telephone the cousin informed about the revealed similar mutation. Patient’s genetic genealogy confirmed the maternal type of inheritance of the disease with incomplete penetrance (Fig. 1).

Nothing special was noted about patient’s neurological status.

Visometry, tonometry, dynamic perimetry, biomicroscopy, optic coherent tomography (OCT) of the posterior ocular segment were performed. Visual acuity of both eyes was 0.005 (counting fingers near the face), perimetry findings revealed bilateral central scotomas. Tonometric intraocular pressure according to Maklakov (10 g load) was found to be 18 mm Hg for both eyes. Reaction of the pupils to the light was vivid. The structures of the anterior ocular segment were without pathological changes. Eye fundus examination showed optical nerve discs to be waxy-pale, the borders to be slightly blurred, excavation — within the norm.

Macular zone of the retina and optical nerve area were studied by OCT technique using optical coherent tomography Cirrus 4000 (Carl Zeiss, Germany) and programs RNFL

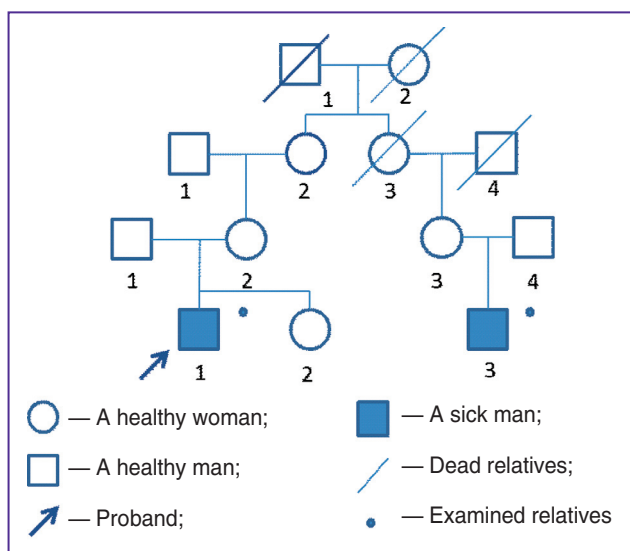


Fig. 1. Genealogy of patient D.

Table 1

Findings of studying retina macular zone of patient D. by OCT technique

Characteristics of macular zone	Right eye	Left eye	Norm
Neuroepithelium thickness in fovea, μm	211	203	220.5–294.8
Mean thickness of the retina parafovealarly, μm	230	228	257.1–295.0
Mean thickness of the retina parafovealarly, mm ³	8.2	8.1	9.39–10.75

Table 2

Findings of studying optical nerve disc of patient D. by OCT technique

Characteristics of optical nerve disc	Right eye	Left eye	Norm
Mean thickness of peripapillar layer of nervous fibers, μm	51	50	75.0–107.2
Symmetry of peripapillar layer of nervous fibers, %	73		76–95
Thickness of peripapillar layer of nervous fibers, μm:			
temple quadrant	45	44	45.1–82.2
upper quadrant	55	56	88.9–136.7
nasal quadrant	50	50	50.0–86.2
lower quadrant	52	52	89.4–138.3

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Thickness analysis, Macular thickness. The results of measuring reticular parameters and nervous fiber layer (Table 1 and 2, Fig. 2–5) were compared with normal values [5, 6]. For clarity, findings of studying the posterior ocular segment without pathology of the retina and optical nerve are also presented (Fig. 2, 3, 6). It was established, that the retina thickness and the neuroepithelium volume in the macular

zone were reduced for both eyes, the most marked reduction of the peripapillary layer of the nervous fibers being noted in the upper and lower quadrants. According to the OCT examination the following conclusion was made: “partial atrophy of optical nerve discs of both eyes”.

On the basis of the characteristic data of history-taking, genealogy, objective clinical picture, and medico-genetic

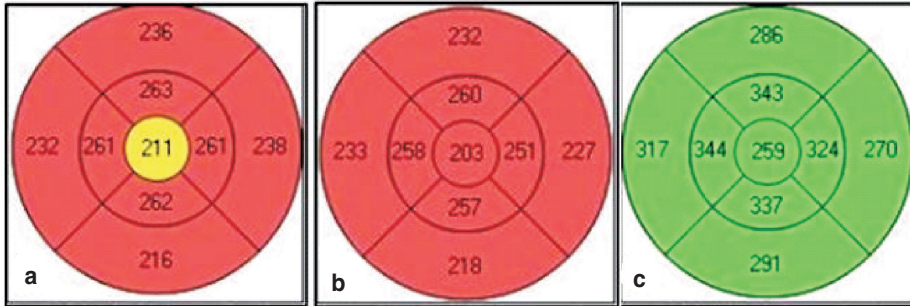


Fig. 2. Thickness of the retina epithelium (in μm) is reduced in all 9 segments of the macular zone of the right (a) and left (b) patient's eye. Compare (c) for the patient without any eye pathology

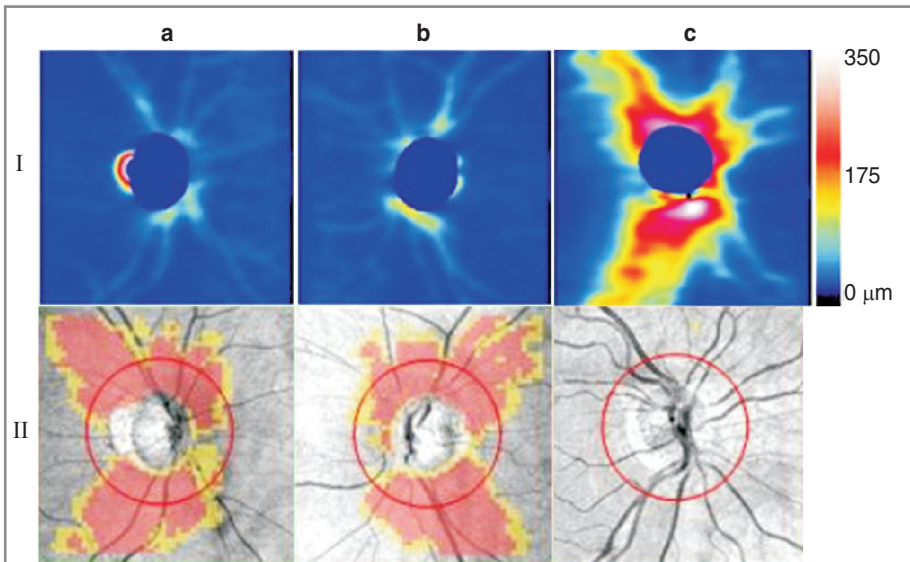


Fig. 3. The area of optical nerve disc of the right (Ia, IIa) and left (Ib, IIb) eye of patient D. Compare Ic, IIc for the patient without eye pathology. The upper row shows color retina mapping according to the thickness of the nervous fiber layer (the scale is given on the right), the lower row presents plane OCT-scans of the retina indicating places of thinned nervous fiber layer: yellow color designates border-line values for the given segment, red is for values below the norm

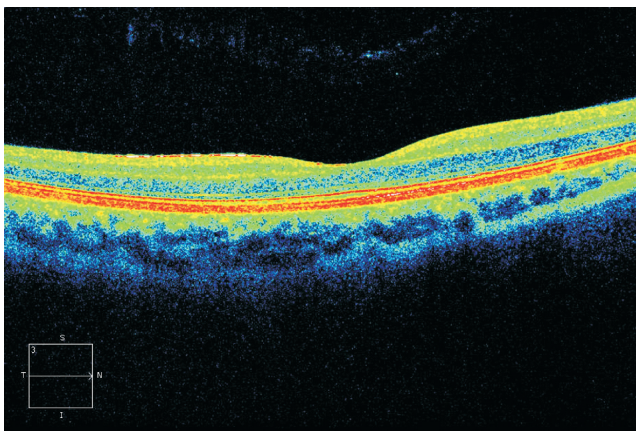


Fig. 4. Horizontal OCT-section through the right eye macula of patient D. Foveolar contour is smoothed. All layers are differentiated, and thinned. The layer of pigment epithelium is homogeneous. Consolidation of the inner border membrane is determined

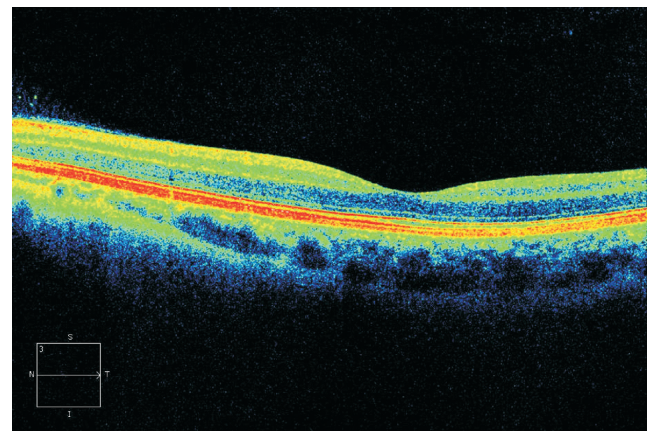


Fig. 5. Horizontal OCT-section through the left eye macula of patient D. Foveolar contour is smoothed. All layers are differentiated, and thinned. Pigment epithelium layer is homogeneous

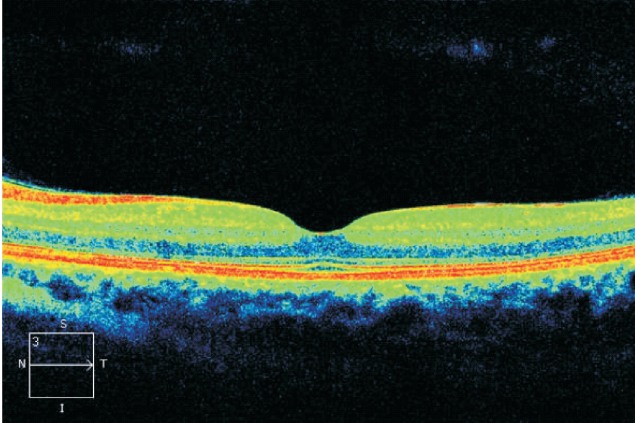


Fig. 6. Horizontal OCT-section of the retina is normal. Foveolar contour is not changed. All layers are differentiated, thickness is within the norm. Pigment epithelium layer is homogeneous

investigation the diagnosis of “Leber hereditary optic neuropathy, atrophic stage” was made.

The administered treatment consisted of: idebinone 30 mg 3 times a day after meals, and levocarnitin 250 mg 3 times a day as a course of 6 weeks duration.

Repeated consultation in 6 months did not reveal any dynamics of the objective indexes.

Leber hereditary optic neuropathy was one of the causes of progressive vision reduction at the young age. The case presented brightly illustrates the difficulty of making timely diagnosis: 9 months passed from the moment of central scotoma appearance till the establishment of clinical diagnosis, the patient was examined and treated with other diagnoses in 6 different medical settings. To suggest a rare disease in a patient

it is necessary to have a clear idea of its clinical picture and the feasibilities of modern diagnostic techniques. The clinical observation described may help a practicing physician to understand better such a rare disease as Leber hereditary optic neuropathy.

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