Leber's hereditary optic neuropathy - case report

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Abstract

Leber's hereditary optic neuropathy is a neuro-ophthalmological entity characterized by acute or subacute bilateral, not simultaneous visual loss with centro cekal scotoma and occasional further visual improvement. This rare ophthalmological disease can be accompanied with dyschromatopsia. It is associated with a matrilineal inheritance pattern. Its diagnosis used to be solely clini¬cal, aided by imaging and neuro-physiological studies, until the advent of descriptions of mitochondrial biochemical abnormalities and genetic testing. We describe a case of 24 year old male with progressive painless deterioration of visual acuity and positive family history.

Keywords: optic neuropathy, Leber, visual acuity

Introduction

Leber's hereditary optic neuropathy is a neuro-ophthalmological entity characterized by acute or subacute bilateral, not simultaneous visual loss with centro cekal scotoma and occasional further visual improvement. This rare ophthalmological disease can be accompanied with dyschromatopsia. It is associated with a matrilineal inheritance pattern. Its diagnosis used to be solely clinical, aided by imaging and neuro-physiological studies, until the advent of descriptions of mitochondrial biochemical abnormalities and genetic testing. Primary point mutations occur at nucleotide positions 3460, 11778 and 14484 of the mitochondrial genome coding for protein subunits of the respiratory chain complexes. The 11778 mutation is most frequently observed, accounting for 80-90% of described cases.2 Young males are primarily affected (80-90%), usually in their third decade of life. Females, carriers of the disease, rarely express the symptoms.

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Case report

A young man adult of 24 experienced a sudden progressive, painless decreasing of visual acuity of the right eye. The condition deteriorated over a few days. He also noticed that the colors when viewed with the right eye, were extremely pale. The left on the first examination was with normal visual acuity. For 22 days visual acuity of the left eye decreased. He had a healthy younger brother, with no visual disturbances. His mother remembered that his uncle (her brother) was 23 years old and had similar problem The patient did not smoke, nor did he consume any alcohol and was well nourished. He was not exposed to heavy metals. At the time of the referral, two months after the onset of the disease, visual acuity was 0.01 in the right eye, and 0.1 in the left. During visual field testing, centrocoecal scotoma on the right eye and central scotoma on the left eye were found (Figure 1). Subjectively present profound dyschromatopsia could not be objectively proved due to very low central vision. Pupillary responses were normal, and relative afferent pupillary defect could not be detected. There were no signs of intraocular inflammation and intraocular pressure was normal. Fundoscopic appearance was not impressive. The only thing that could be seen was slightly tortuous

papillary capillary network and very discrete dilatation and tortuosity of small peripapillary vessels, more pronounced on the right eye. On fluorescein angiography, the vessels were intact, with no leakage (Figure 2). Pattern visual evoked potentials (VEP) were bilaterally almost extinct, with hardly discernible P100. Retrobulbar part of optic nerve showed no abnormalities on orbitalechography. Standard imaging studies (CT, MRI) excluded the presence of chiasmal or other intracranial mass lesion as well as foci of demyelinisation. The presence of sarcoidosis, tuberculosis and syphilis was also excluded with the appropriate serological tests and chest radiography. Peripheral blood sample was taken for mitochondrial DNA (mt DNA) isolation from leukocytes. A G11778A mutation was found in leukocyte mtDNA and the mutation was homoplasmic. This finding confirmed earlier presumptive diagnose of LHON. Follow-up showed no improvement of central visual acuity for almost a year, but thereafter the left eye vision started to improve. On the last check-up, 14 months after the onset of the disease, left eye visual acuity recovered to 0.7 but the right eye stayed at 0.1. On ophthalmoscopy, bilateral profound optic atrophy with empty, pale discs was found (Figure 3). On control pattern VEP there were no changes. The mother`s leukocyte mt DNA has already been isolated and sent for analysis. We hope to get consent from other family members to perform studies on their mitochondrial genome. During outpatient follow-up, his symptoms have not increased or decreased, and he has been medicated using vitamin C (500 mg t. i. d.), vitamin B1 (5 mg), vitamin B2 (2 mg), vitamin B6 (2 mg), vitamin PP (20 mg), vitamin

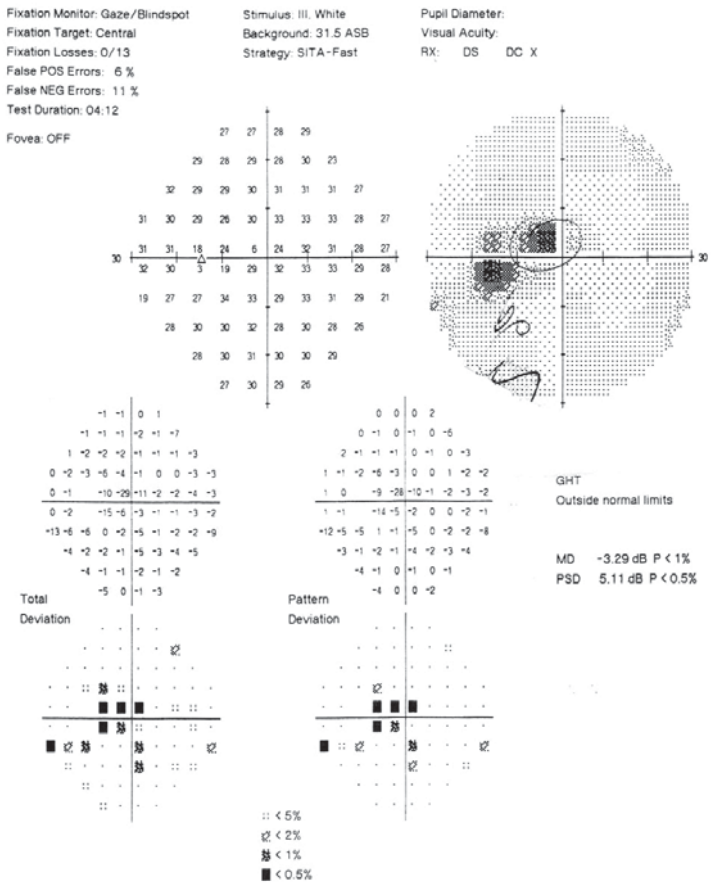

FIGURE 1. Centrocoecal scotoma on the right eye and central scotoma on the left eye

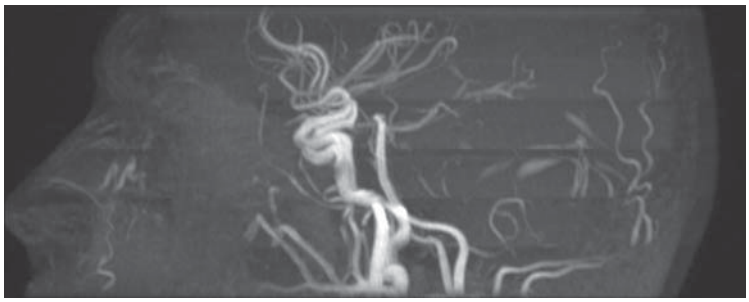

FIGURE 2. Intact vessels on fluorescein angiography

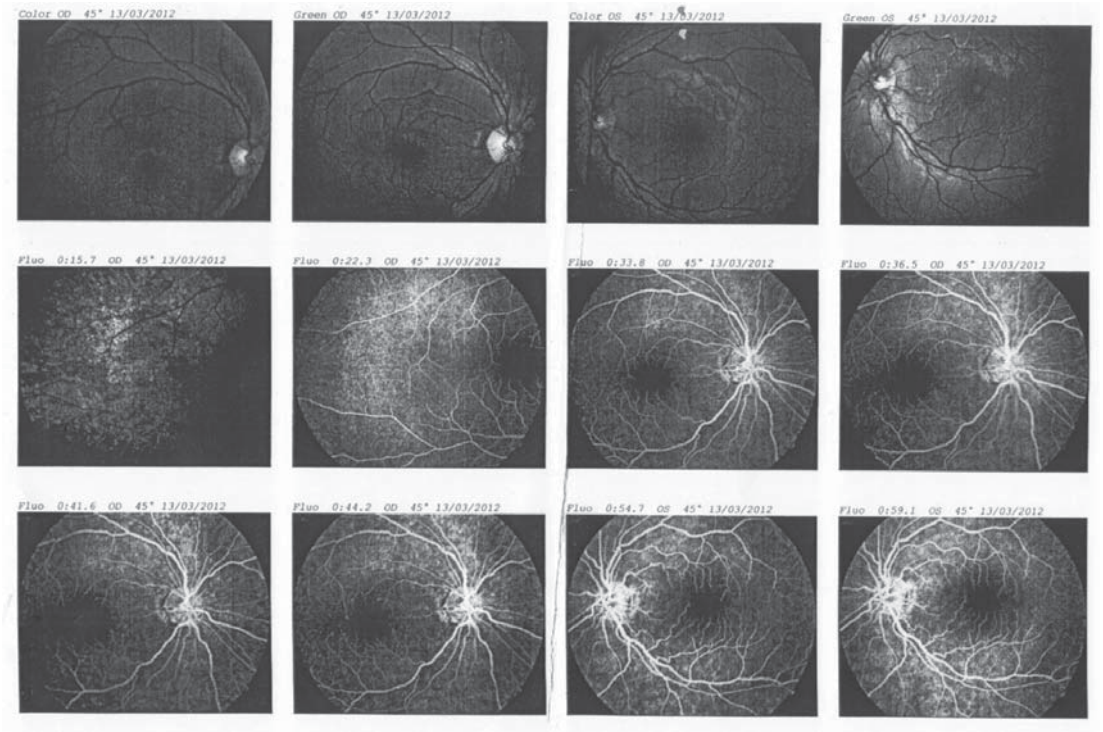

FIGURE 3. Bilateral profound optic atrophy with empty, pale discs on ophthalmoscopy

B5 (3 mg), in one tablet, t .i. d, and coenzyme Q10 (100 mg b .i .d.). The purpose of this supplementation was to improve cellular ATP usage.

Discussion

Hereditary optic neuropathies are a group of diseases with defined clinical presentation and different inheritance patterns. The clinical setting may be of acute, sub-acute or relentlessly progressive painless visual loss, bilateral (simultaneous or sequential), with centro cecal scotoma, altered color perception (dyschromatopsia) and optic atrophy. The inheritance pattern may present as autosomal dominant, recessive, X-linked or matrilineal (1). In Leber's hereditary optic neuropathy, male individuals in their teens or twenties suffer acute visual loss that is sequential in 78% of cases and simultaneous in 22% (2). Fundus examination in the initial stages shows papilledema and peripapillary microangiopathy, evolving to atrophy of the nerve fiber layer of the retina and finally leading to optic atrophy and centrocecal scotoma (3). Family history is suggestive of maternal inheritance in 50% of patients, and in the other 50% the disease seems to be sporadic (4). Four main mutations of mitochondrial DNA (mtDNA) encompass over 90% of patients with Leber's hereditary optic neuropathy: 11778 (genetic subunit ND4), 14484 (ND6), 3460 (ND1) and 14459 (ND6). The mutation at 14459 corresponds to the dystonia phenotype for Leber's hereditary optic neuropathy (5). Mashima et al.6 assessed the prevalence of different mutations in a sample of 80 individuals with Leber's hereditary optic neuropathy and showed that 87% carried the mutation at 11778, 9% at 14484 and 4% at 3460. Riordan-Eva et al. 2 found prevalence for the same mutations of respectively 75%, 15% and 8%. Oriental studies demonstrate higher proportions of 11778 mutations than do Western studies (6,7). Biousse et al. (8) reported the 14484 mutation on monozygotic twins with distinct phenotypes (only one symptomatic sibling), while genetic testing in the mother was negative, thereby suggesting de novo mutation. Sadun et al. recently published that there is the strong influence of environmental risk factors,

with smoking as the most common factor (9). Multiple sclerosis (or MS-like disease) shares a rather uncommon comorbidity with Leber's hereditary optic neuropathy. Some patients with Leber's hereditary optic neuropathy develop clinical features that are phenotypically indistinguishable from multiple sclerosis, and mutations for Leber's neuropathy are considered to be a risk factor in the pathophysiology of multiple sclerosis (10,11). On the other hand, prevalence studies among multiple sclerosis patients have failed to demonstrate primary mtDNA mutations (12,13). It is currently recommended to proceed with mt DNA analysis for all young male multiple sclerosis patients with initial neuro-ophthalmological manifestations and peripapillary microangiopathy, especially those with bilateral symptoms and a positive family history for visual los (14). There is no specific treatment for Leber's hereditary optic neuropathy. From an empirical standpoint, most if not all patients will receive an initial diagnosis of optic neuritis and will be treated, without any response, using steroid therapy at high doses. In a case-control study with patients carrying mutations 14484, 3460 and 11778, combination therapy using idebenone / vitamin B2/vitamin C (which improves ATP availability) shortened the time required for vision recovery in the group using this therapy (11.1 months), in comparison with the placebo group (17.4 months; $p = 0.03$) (15). A single-patient study backed by magnetic resonance spectroscopy of the central nervous system (31P-MRS) showed clinical and imaging improvement When idebenone treatment was instituted (idebenone is not available in Brazil, but only in Argentina: its action is similar to that of the coenzyme Q10) (16). The prognosis for vision recovery depends on the mutation reported. Good prognosis may be found in up to 50% of patients bearing the 14484 mutation. Nevertheless, only 4% of patients with the 11778 mutation have gradual improvement, as we were able to observe in our patient (17).

Conclusion

A diagnosis of Leber's hereditary optic neuropathy should be suspected whenever young males develop bilateral visual loss, usually sequential, with a positive familial history. Neuro-ophthalmological examination may demonstrate suggestive signs of Leber's hereditary optic neuropathy. The mutation at the 11778 locus is the most frequent mutation of mitochondrial DNA in Leber's hereditary optic neuropathy patients.

Conflict of interest

Authors declare no conflict of interest.

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