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Case Report

A Rare ND5 Mutation Causing Leber's Hereditary Optic Neuropathy

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Leber's hereditary optic neuropathy · ND5 · Mitochondrial DNA

Abstract
Mutations to the ND5 gene are uncommonly associated with Leber's hereditary optic neuropathy (LHON). Herein, we describe a 57-year-old man with the m. 13528A>G, p. (Thr398Ala) mutation at the ND5 gene who presented with progressive bilateral vision loss over the course of 3 months. He had a significant history of smoking and alcohol consumption. Visual field testing demonstrated bilateral central scotomas. At 2-year follow-up, his visual acuity improved relative to baseline and temporal optic disc pallor was observed in both eyes. There are scarce reports of this mutation in the literature, and this case report further expands the clinical presentation of the m. 13528A>G mutation at the ND5 gene in patients with LHON phenotype.

Introduction

Leber's hereditary optic neuropathy (LHON) is a mitochondrial disease that is characterized by painless loss of central vision due to the progressive degeneration of retinal ganglion cells (RGCs) in the papillomacular bundle. In general, LHON tends to affect young males; however, females and all age-groups are also affected. Several mutations to mitochondrial DNA (mtDNA) have been reported in patients with LHON phenotype. However, the three classic point mutations with the highest frequency are nucleotide positions 11778,

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14484, and 3460 [1]. These mutations generally result in dysfunction of complex I of the electron transport chain, thus leading to impaired ATP synthesis and subsequent degeneration of RGCs. Notably, LHON is characterized by incomplete penetrance and does not always manifest in individuals carrying pathogenic mutations. However, certain risk factors (e.g., smoking) can increase the likelihood of developing vision loss [2]. Although the aforementioned mutations are observed most commonly, several other mtDNA mutations affecting mitochondrial function have been characterized in the literature. This case report describes a patient with LHON phenotype with a mutation affecting the ND5 gene [i.e., m. 13528A>G, p. (Thr398Ala)]. The CARE Checklist has been completed for this case report and is attached as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000529423)

Case Presentation

A 57-year-old man was referred for progressive bilateral vision loss over the course of 3 months. The patient's past medical history was significant for newly diagnosed diabetes mellitus. However, he did not take any medications at the time of presentation and his diabetes was diet controlled. He had a 12.5 pack-year smoking history and consumed 5–10 glasses of alcohol per day. The patient primarily followed a vegetarian diet, but occasionally consumed seafood and eggs. Visual acuity on initial examination was 20/500 OD and 20/400 OS. Pupillary examination revealed normal-sized pupils that were sluggish without a relative afferent pupillary defect. Fundus examination demonstrated temporal pallor of the optic nerves. Humphrey visual field testing demonstrated central scotomas in both eyes (Fig. 1). An MRI of the brain and orbits with contrast was found to be normal. A differential diagnosis of bilateral optic neuropathy secondary to nutritional deficiency or LHON was suspected. He underwent a workup that revealed normal B12, RBC folate, complete blood count, and copper levels. Mitochondrial whole genome analysis unveiled a missense variant at 100% homoplasy in the *ND5* gene [m. 13528A>G, p. (Thr398Ala)]. At 24-month follow-up, his visual acuity improved to 20/150 OD and 20/150 OS, and fundus examination demonstrated temporal optic disc pallor OU. Humphrey visual field testing demonstrated bilateral central scotomas and OCT retinal nerve fiber layer (RNFL) showed interval thinning of the temporal portion of the optic nerve (Fig. 2). The importance of smoking and alcohol cessation was emphasized to the patient. In addition, B-complex vitamins were recommended to the patient. At 6 months, he reported that he was no longer smoking cigarettes and had been using nicotine replacement. He had also stopped his alcohol consumption.

Discussion

RGCs are densely packed with mitochondria and demonstrate a high level of metabolic activity. Consequently, impaired ATP synthesis can result in RGC degeneration, which is a characteristic feature of LHON [3]. Complex I of the electron transport chain is composed of 14 core subunits, and 7 subunits are encoded by mtDNA [4]. Pathogenic mutations to the genes that encode any of these subunits may result in complex I dysfunction, thus leading to impaired ATP synthesis. The ND5 gene – which encodes a complex I subunit – has previously been identified as a "mutational hotspot." Moreover, pathogenic mutations to ND5 are associated with several diseases, including Leigh syndrome, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, and LHON [5].

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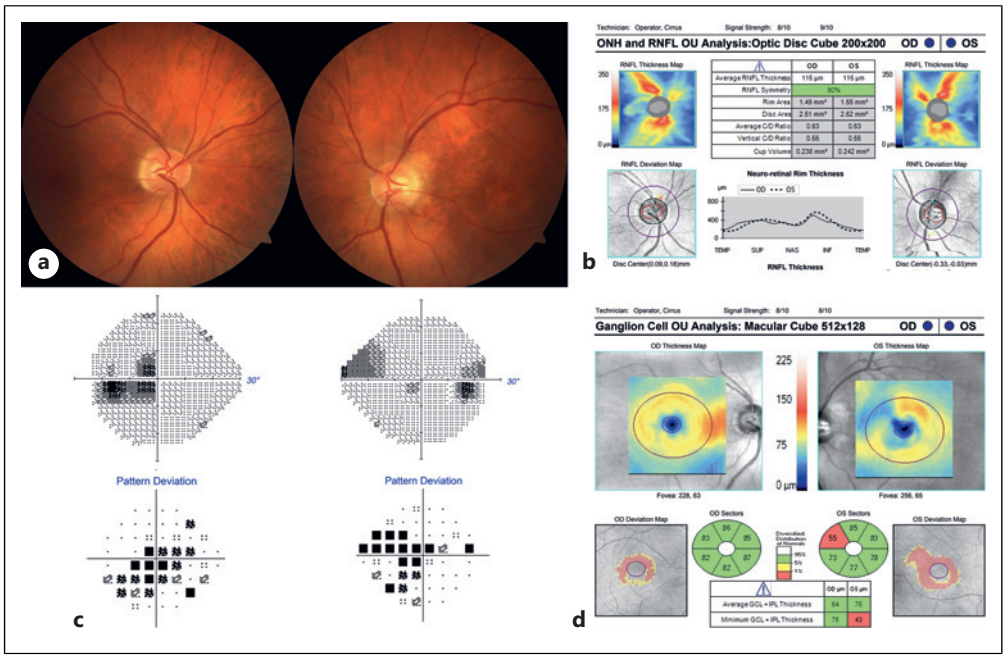

Fig. 1. Fundus photos (**a**) at initial presentation demonstrating mild temporal pallor more obvious in the left eye. Optical coherence tomography (OCT) of the retinal nerve fiber layer (**b**) showed a normal average thickness in both eyes. Humphrey 24-2 SITA-Fast visual fields (**c**) showed central scotomas in both eyes. The stimulus size was III and mean deviation was −10.49dB OD and −7.55dB OS. The visual field index was 76% OD and 79% OS. OCT of the macular ganglion cell-inner plexiform layer (**d**) did not show any significant abnormalities and there was a left segmentation error.

The mutation described in this article (i.e., m. 13528A>G) has been previously described in a small number of case reports. Batandier and colleagues [6] initially described this mutation in two unrelated Caucasian patients from France who exhibited LHON phenotype. One patient was female; however, the gender of the other patient was not described. Additionally, the visual acuities of both patients were not reported, and no further clinical details were provided for these patients. Petruzzella et al. [7] described this mutation in a 44-year-old male with suspected LHON who presented with sudden onset visual impairment in his right eye. Visual field testing in this patient revealed a cecocentral scotoma in the right eye. His visual acuity at initial presentation was 20/40 OD and 20/20 OS, and after 2-month follow-up, the visual acuity improved to 20/25 OD and 20/20 OS. Additionally, RNFL thinning was observed in the nasal quadrant. In contrast, our patient had significantly worse visual acuity at initial presentation (i.e., 20/500 OD and 20/400 OS) and presented at an older age (i.e., 57 years). The final visual acuity in the case described by Petruzzella and colleagues [7] was at 2-month follow-up, whereas the final visual acuity reported in this case report was at 2-year follow-up. Our patient's visual field demonstrated bilateral central scotomas rather than a unilateral cecocentral scotoma. Moreover, temporal – rather than nasal – RNFL thinning was observed in our patient. Given these differences, the case described herein expands the clinical presentation of the m. 13528A>G mutation as there are significant differences with respect to visual function and OCT parameters compared to previously published cases describing this mutation.

Perturbations to protein structure may lead to functional consequences, and the mutation described in this case report leads to a single amino acid substitution (i.e., threonine to alanine) that has the potential to disrupt local residue interactions. Specifically, threonine has a polar side chain as manifest by the presence of a hydroxyl group; moreover, substitution to

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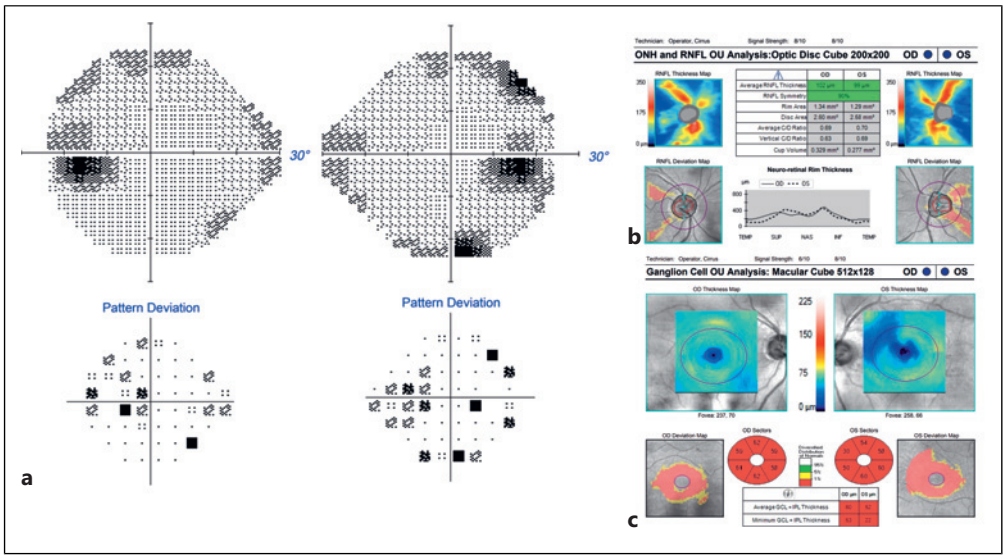

Fig. 2. At final follow-up 24 months after initial presentation, Humphrey 24-2 SITA-Fast visual fields (**a**) showed less dense central scotoma. The stimulus size was III and mean deviation was −8.69dB OD and −6.22dB OS. The visual field index was 88% OD and 89% OS. OCT of the retinal nerve fiber layer (**b**) showed temporal thinning in both eyes and there was diffuse thinning in the ganglion cell layer-inner plexiform layer (**c**).

alanine – a nonpolar residue – can lead to loss of hydrogen-bonding, thus compromising ND5 protein structure. A study that examined the biochemical implications of the m. 13528A>G mutation observed a significant decrease in the levels of detectable ATP in affected tissue due to complex I dysfunction. Additionally, oxidative stress due to mitochondrial dysfunction was manifested by elevated reactive oxygen species levels in fibroblasts [7]. Taken together, there is compelling evidence to support the pathogenicity of this mutation.

Although LHON does not manifest in all individuals carrying pathogenic mutations, there are certain risk factors that may precipitate the onset of vision loss. Our patient had a significant history of smoking and alcohol consumption, both of which have been implicated in precipitating vision loss in individuals carrying LHON mutations [1, 2]. Therefore, it is crucially important to recommend smoking cessation and a reduction in alcohol consumption in patients at risk for developing phenotypic LHON due to the presence of pathogenic mutation(s). Ultimately, the presence of the m. 13528A>G mutation – which has previously been implicated in LHON – in conjunction with the presence of both risk factors (i.e., smoking and alcohol consumption) favor a diagnosis of LHON in this patient.

In conclusion, this case report describes a patient with LHON phenotype who carried the m. 13528A>G mutation, providing further evidence to support the pathogenicity of the m. 13528A>G mutation in LHON. Additionally, this case report further expands the clinical presentation of the m. 13528A>G mutation due to the differences observed in our case compared to previously published cases.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval is not required for this study in accordance

with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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Author Contributions

Bhadra U. Pandya, Amir R. Vosoughi, Aaditeya Jhaveri, and Jonathan A. Micieli: conception and design, acquisition of data, analysis and interpretation of data, preparation of the manuscript, and final approval of the completed manuscript.

Data Availability Statement

All available data are included in this article. Further inquiries can be directed to the corresponding author.

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