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Case Report

Clinical variability in hereditary optic neuropathies: Two novel mutations in two patients with dominant optic atrophy and Wolfram syndrome

Alberto Galvez-Ruiz

Abstract

Dominant optic atrophy (DOA) and Wolfram syndrome share a great deal of clinical variability, including an association with hearing loss and the presence of optic atrophy at similar ages. The objective of this paper was to discuss the phenotypic variability of these syndromes with respect to the presentation of two clinical cases.
We present two patients, each with either DOA or Wolfram syndrome, and contribute to the research literature through our findings of two novel mutations.
The overlapping of several clinical characteristics in hereditary optic neuropathies can complicate the differential diagnosis. Future studies are needed to better determine the genotype-phenotype correlation for these diseases.

Keywords: Hereditary optic neuropathies, Dominant optic atrophy, Wolfram syndrome, Diabetes mellitus, Deafness

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Introduction

In hereditary optic neuropathies, the differential diagnosis is broad. However, Dominant Optic Atrophy (DOA) and Wolfram syndrome (WS) share significant clinical variability, including an association with hearing loss and the presence of optic atrophy at similar ages (first decade of life).[1–3]

We present two cases of patients with either DOA or WS, and we contribute to the research literature through our findings of two novel mutations.

The objective of this work was to comment on the phenotypic variability of these syndromes with respect to the presentation of two clinical cases.

Case reports

Patient 1

Female patient, 25 years of age with refractive error since puberty (average myopia in both eyes) (OU) admitted to the hospital for possible refractive surgery.

Upon pre-surgery evaluation, bilateral temporal papillary pallor is detected, so the patient is referred to the Neuro-ophthalmology unit for study. The patient has no family history of vision loss and does not present with hearing loss or any other neurological symptom. There is a family history of consanguinity.

On ophthalmic examination, the patient presents a visual acuity (VA) of 0 (logMAR units) OU with correction. The

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Neuro-ophthalmology Unit, King Khaled Eye Specialist Hospital, P.O. Box 7191. Riyadh 11462, Saudi Arabia
Neuro-ophthalmology Unit, Ruber International Hospital, Madrid, Spain
e-mail address: Algarui@yahoo.com

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patient is able to identify 14 of 15 plates in the Ishihara test with OU. The pupils are isochoric, normoreactive to light and accommodation, and no relative afferent pupillary defect (RAPD) is detected. The ocular fundus shows a congenitally anomalous papilla with temporal pallor in OU (Fig. 1). Optical coherence tomography (OCT) of the optic nerve (RTVue Premier Optovue) performed for the patient showed a reduction mainly in the temporal portion of the retinal nerve fiber layer (RNFL) thickness in OU (Fig. 2).

Magnetic resonance imaging (MRI) of the skull base and orbits is normal. The Humphrey visual field (HVF) testing (SITA-fast 30-2) shows a normal result in the OD (mean deviation −0.96 dB) and some isolated scotomas in the OS (mean deviation −3.01 dB). The result for the OS may be unreliable due to the excess of false positives (Fig. 3). The genetic analysis requested shows that the patient is a heterozygous carrier of the missense mutation p.Tyr917His (c.2749T > C) in the optic atrophy 1 (OPA1) gene, which is diagnostic for DOA. The result was confirmed by sequencing of an independent PCR product (polymerase chain reaction). Also, two bioinformatics tools conducted predicted a pathogenic character for this mutation. To our knowledge, this mutation has not been described previously in the literature. After over a year of follow-up, the patient has remained clinically stable.

Patient 2

Female patient, 20 years old, comes to the office following a neuro-ophthalmology consultation after presenting with decreasing VA since childhood. The patient was also diagnosed with diabetes mellitus (DM) at 3 years of age. The patient does not present with hearing loss or any other associated neurological symptoms or show signs or symptoms of diabetes insipidus (DI). The patient has no family history of vision loss, although there is a family history of consanguinity.

On ophthalmic examination, the patient has a VA of +1.0 (logMAR) in the right eye (OD) and of +1.6 (logMAR) in the left eye (OS). The pupils are isochoric, normoreactive to light and accommodation and without RAPD. The fundus shows bilateral temporal pallor with normal maculae in OU (Fig. 4). The GVF demonstrates the existence of a bilateral cecocentral defect. Cranial MRI of the orbits is normal. The patient presents normal plasma and urine osmolalities. The genetic study requested shows that the patient is homozygous for the c.1046_1047delinsAG p.Ile349Lys mutation in exon 8 of the Wolfram syndrome 1 (WFS1) gene, which is diagnostic for WS. To our knowledge, this variant has not been described previously. Also we conducted OPA1, OPA3 and OPA7 genetic tests for the patient, resulting all of them negative. After over a year of follow-up, the patient has remained clinically stable without the onset of new symptoms.

Discussion

In the present article, we report two clinical cases of hereditary optic neuropathy: a patient diagnosed with DOA carrying a novel mutation in the OPA1 gene but with virtually no visual symptoms; and another patient diagnosed with WS due to a novel mutation in the WFS1 gene but without deafness or DI. Both patients show significant clinical variability in these entities, presenting with phenotypically atypical or incomplete clinical cases.

DOA typically manifests as the insidious loss of VA in the first decade of life.[1,4] On ophthalmic examination, pallor of the temporal sector of the optic nerve is demonstrated with excavation that can simulate glaucoma.[1,5] On visual field testing, central or cecocentral scotomata are characteristic.[1,6] There are also patients with a phenotype designated DOA plus, which can be associated with sensorineural hearing loss, myopathy, peripheral neuropathy, ataxia, symptoms that mimic multiple sclerosis and spastic paraplegia.[1,7]

The majority of DOA cases are caused by mutations in the OPA1 gene (50–60% of patients). Specifically, more than 200 pathogenic mutations have been described in the OPA-1 gene. However, in large-scale studies, some families with DOA have had mutations associated with other chromosomal loci: OPA-3, OPA-4, OPA-5, and OPA-7,[8–10]

The OPA1 gene encodes a protein (dynamin-related GTPase) of the inner mitochondrial membrane. Its absence or dysfunction results in an alteration in the mitochondrial DNA stability as well as the integrity of the mitochondrial respiratory chain.[11]

One of the main clinical characteristics of DOA is its great clinical variability: there are patients with isolated visual repercussions (such as the patient we present here) while others experience legal blindness; there are clinical presentations that exclusively affect the optical nerve, and there are syndromic forms with multiple neurological symptoms (20% of all patients). This interfamilial and intrafamilial phenotype variability is explained in part by the different degrees of penetration of DOA, which has been calculated to be approximately 70%.[1] However, it is also due to the presence of mitochondrial DNA deletions caused by nuclear mutations in the OPA1 gene. Thus, DOA is considered a mitochondrial

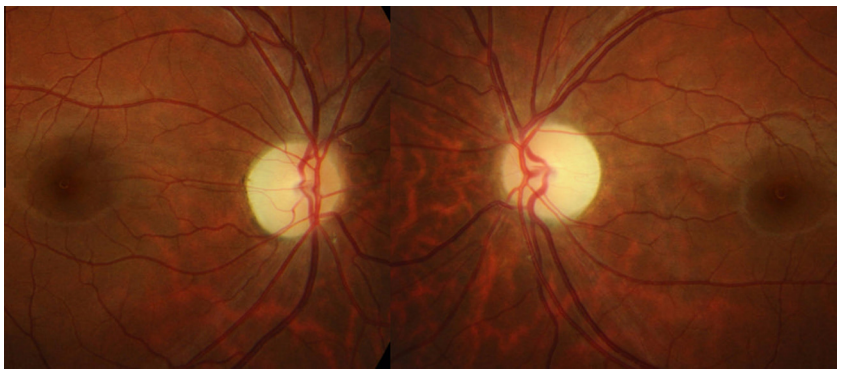

Figure 1. Fundus of patient 1 showing congenitally anomalous papilla with temporal pallor in OU.