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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

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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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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

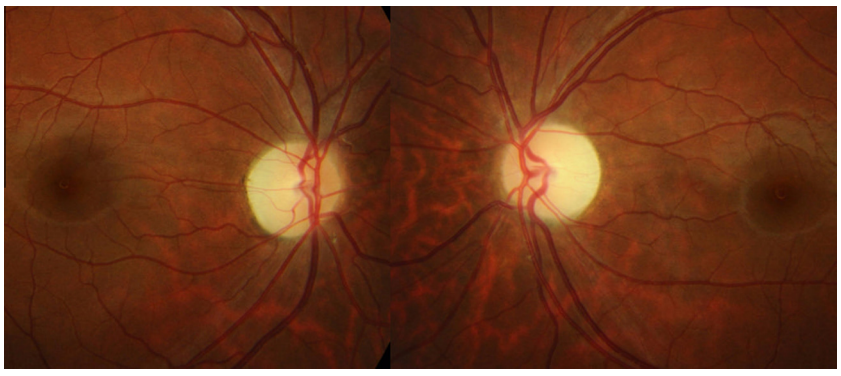

Figure 1. Fundus of patient 1 showing congenitally anomalous papilla with temporal pallor in OU.

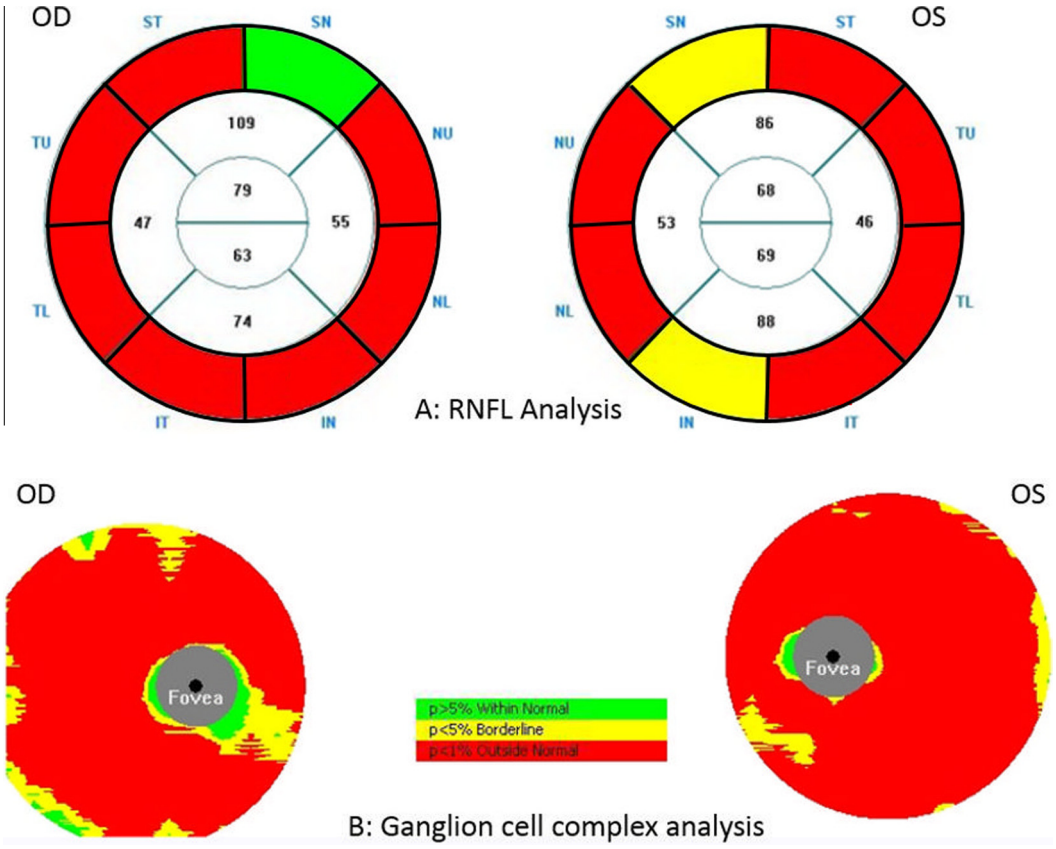

Figure 2. Optical coherence tomography (OCT) of the optic nerve (RTVue Premier Optovue) showing a reduction mainly in the temporal portion of the retinal nerve fiber layer (RNFL) thickness in OU. The mean RNFL average for the OD was 71 μm and for the OS 68 μm (A). We include also the Ganglion Cell complex thickness analysis (B), which is reduced in OU (Average thickness Ganglion cell complex OD: 62 μm and OS: 56 μm).

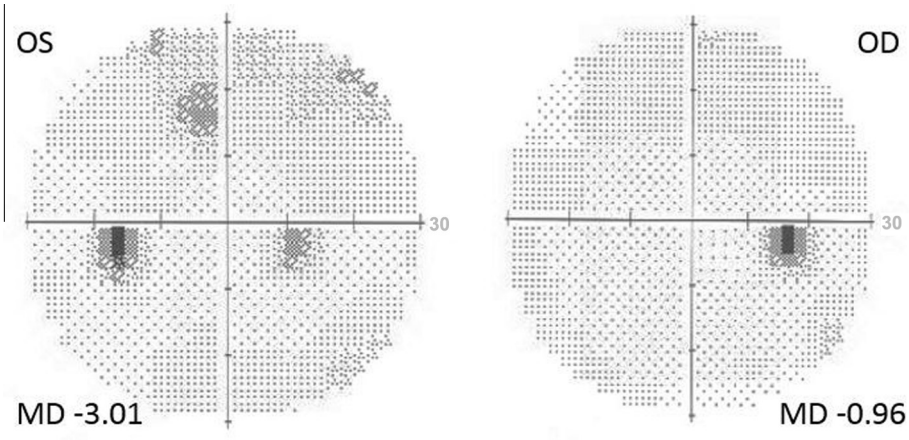

Figure 3. Humphrey visual field (HVF) testing (SITA-fast 30-2) showing a normal result in the OD (mean deviation −0.96 dB) and some isolated scotomas in the OS (mean deviation −3.01 dB). The result for the OS may be unreliable due to the excess of false positives.

disease and it reflects the great clinical variability of mitochondrial syndromes.[1]

The case of our patient with virtually no visual symptoms and with incipient optic nerve pallor is one of the mildest extremes on the spectrum of presentation of DOA. Normally, this type of virtually asymptomatic patient is discovered when performing a genetic analysis on the relatives of a patient with DOA. In our patient, the diagnosis was suspected when the optic nerve pallor was discovered on workup prior to refractive surgery.

Regarding WS, in its original description, DM and optic atrophy that are present from an early age in life are mentioned as characteristics. In later descriptions, the presence of DI and hearing loss was added.[12] Thus, this syndrome is also known by the acronym DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness). Approximately 50% of patients present with the complete phenotype.

DM and optic atrophy have an average age of onset of 10 years. Hearing loss is present in 66% of individuals with

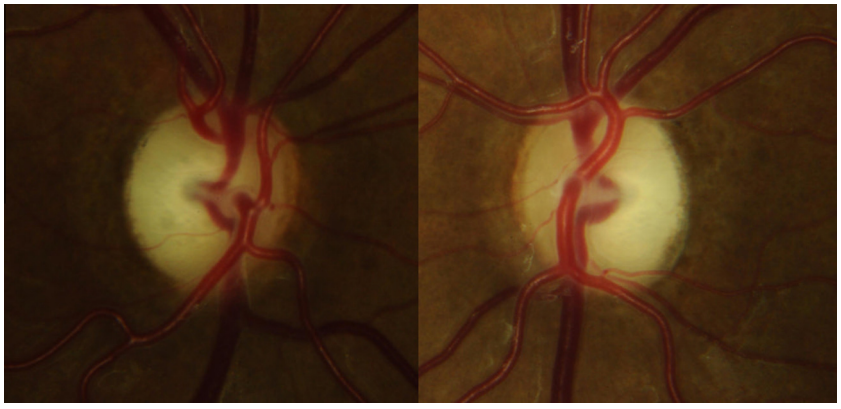

Figure 4. Fundus of patient 2 showing bilateral temporal pallor with normal maculae in OU.

an average age of onset of 12.5 years. DI occurs in 72% of individuals with an average age of onset of 15.5 years. Other neurological alterations that may be present in these individuals include ataxia, apnea, dementia and psychiatric disorders.[13]

In 1997, the WSF1 gene was identified in the 4p16.1 region. The majority of mutations in patients with WS are inherited recessively and are located in exon 8, but mutations have also been described in exons 3, 4, and 5.[13]

The WFS1 is a transmembrane protein of the endoplasmic reticulum (ER). This organ controls the folding of cellular proteins. Under physiological conditions, the accumulation of unfolded proteins provokes WFS1 to stop translating proteins, activating the chaperones responsible for protein folding. However, if the accumulation of unfolded proteins persists (as is the case in WFS1 deficiency), cell apoptosis is induced.[14]

Mutations in the WFS1 gene are responsible for a wide phenotypic spectrum: in addition to classic WS, they have been described as WS-like (associated with deafness, DM, psychiatric alterations and in some cases, optic atrophy)[1] and the syndrome of sensorineural deafness associated with WFS1 that presents in isolation. Also, WS type 2 has recently been described in 4 Jordanian families, characterized by optic atrophy, DM and deafness but not DI. It is caused by mutations in the CDGSH iron sulfur domain 2 (CISD2) gene (located on chromosome 4q22).[1]

Interestingly, similar to patients with OPA1 mutations, deletions in mitochondrial DNA have been described in WS. This finding perhaps also explains the great variability in clinical expression present in WS, which is similar to the wide phenotypic spectrum of diseases of mitochondrial origin.[1]

Our patient with WS, despite having an age of 20 years, presents only part of the clinical spectrum of the syndrome (DM diagnosed at 3 years and optic atrophy). It should be considered that the mutation the patient carries (causing changes in a single amino acid) likely entails a more benign phenotype expression. However, it is necessary to follow the patient for years to determine definitive clinical expression.

In summary, we present the cases of two patients each carrying novel mutations in either the OPA1 or WSF1 genes that represent good examples of the significant intra- and interfamilial clinical variability that can occur in hereditary optic neuropathies. This variability is due in part to the different mutations in the OPA1 and WFS1 genes and to their different degrees of penetration. However, the fact that both mutations are in some cases related to mitochondrial DNA deletions potentially partially explains this variability. However, there is no complete scientific explanation at present for this variability, and future research will be needed to continue to clarify its source.

Similarly, the overlap between certain clinical characteristics in several of these syndromes (such as optic atrophy and hearing loss) delays diagnosis in some patients (especially in patients with phenotypes that vary from the classical presentations).

Conflict of interest

The authors declared that there is no conflict of interest.

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