Autosomal Dominant Optic Atrophy Plus Syndrome

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Autosomal Dominant Optic Atrophy Plus Syndrome

Abstract

Background: Dominant optic atrophy (DOA) is the most commonly encountered hereditary optic neuropathy in clinical practice and is the result of a mutation in the OPA1 or OPA3 genes encoding mitochondrial membrane proteins. The resultant mitochondrial dysfunction causes a distinct set of ophthalmic findings and may progress to extra-ocular systems known as OPA plus syndrome. We present a case of late-onset OPA plus syndrome encompassing both typical ophthalmic findings and the rarer extra-ocular findings. Case Report: A 41 year-old Caucasian male presents for a second opinion regarding a previously diagnosed traumatic optic neuropathy. Examination revealed decreased best-corrected acuities, optic nerve pallor, optical coherence tomography thinning of the retinal nerve fiber layers, progressive centrocecal visual field defects and tritanomalous color vision defects. All findings proved to be bilateral and symmetric. As the ophthalmic findings were inconsistent with a traumatic optic neuropathy, genetic testing was pursued resulting in a DOA diagnosis. Specialty consults demonstrated high-frequency hearing loss and mitochondrial myopathy consistent with OPA plus syndrome. Conclusion: While not a common diagnosis, hereditary optic neuropathies are most likely to present initially to primary eye care. The practitioner should be familiar with the ophthalmic findings and the need for specialty consult should a DOA diagnosis be confirmed.

Keywords
Kjer's, Autosomal Dominant Optic Atrophy, ADO Plus

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Introduction

Autosomal dominant optic atrophy (DOA) was first described by the Danish ophthalmologist Dr. Poul Kjer in 1959 and initially termed Kjer’s Optic Atrophy. DOA is a neuro-ophthalmic condition attributable to bilateral optic nerve degeneration and is characterized by insidious vision loss that may be variable in both onset and severity, centrocecal scotomas, characteristic color vision defects, and phenotypic variability. DOA prevalence varies geographically but affects at least 1 in 35,000 within the general population, distinguishing it as the most commonly encountered hereditary optic neuropathy in clinical practice. A significant subset of DOA patients may progress to a “plus” syndrome following visual symptoms which may involve sensorineural hearing loss, myopathy, chronic progressive external ophthalmoplegia, ataxia, or neuropathy. We present a case of DOA syndrome originally diagnosed as traumatic optic neuropathy with a subset of plus syndrome neurological abnormalities. Although a family history is nearly always ubiquitous, the patient is without a discernable pedigree for either ophthalmic or neurologic characteristics of DOA.

Case Report

A 41-year-old Caucasian male presented for a second opinion regarding a diagnosis of traumatic optic atrophy. The patient reported a history of traumatic optic atrophy following a blast exposure fifteen years prior while serving in the United States Armed Forces. He reported excellent vision prior to the incident, but vision had been reduced since that time. Ocular history was otherwise unremarkable, as was his family ocular history. His medical history was significant for sleep apnea, post-traumatic stress disorder, panic disorder, unspecified memory loss, hypertension, well-controlled type II diabetes mellitus, migraines, medication-induced postural tremor, and episodic ataxia. Relevant medications included metformin, zolmitriptan, sertraline and quarterly botox injections for migraine prophylaxis.

Best-corrected Snellen visual acuities were 20/30² OD and OS. Preliminary testing demonstrated normal pupils and extraocular muscle movement, while pseudoisochromatic plates [Ishihara 24 plate edition; Graham-Field, Atlanta GA] revealed a mild deuteranomalous defect in both eyes. Anterior segment and tonometry were unremarkable bilaterally. A dilated funduscopic examination (DFE) revealed a 2+ temporal wedge of pallor on each optic disc without excavation (Figure 1). Fundus photos were obtained [Topcon 50DX; Topcon, Oakland, NJ].
A retinal nerve fiber layer optical coherence tomography (OCT) was similarly obtained demonstrating widespread, symmetric temporal thinning bilaterally [Spectralis; Heidelberg Engineering, Heidelberg, Germany].

A diagnosis of bilateral optic neuropathy was established. Subsequently, an extensive social history proved negative for tobacco use, excessive ethanol consumption, recreational drug abuse, or heavy metal exposure. A basic optic neuropathy lab panel and magnetic resonance imaging (MRI) of the brain and orbits with gadolinium contrast were initiated and proved unremarkable (Table 1, Figure 3).
<table>
<thead>
<tr>
<th>Study</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>complete blood count with differentials</td>
<td>unremarkable</td>
</tr>
<tr>
<td>basic metabolic profile</td>
<td>unremarkable</td>
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<tr>
<td>treponema pallidum antibody serum test</td>
<td>non-reactive</td>
</tr>
<tr>
<td>vitamin B12 / Folate</td>
<td>normal range</td>
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<tr>
<td>serum lysozyme</td>
<td>normal range</td>
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<tr>
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<td>non-reactive</td>
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<td>anti-nuclear antibodies</td>
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</table>

Table 1 laboratory investigations

Automated perimetry (HVF) with 24-2 threshold visual fields (Figure 4) detected symmetric centrocecal scotomas better characterized with 10-2 threshold visual fields (Figure 5) [Humphrey Field Analyzer III; Carl Zeiss Meditec Inc., Dublin, CA].
The diagnosis of bilateral optic neuropathy was reaffirmed, although the etiology was still in question. A three-month follow up was scheduled. The return visit elicited a complaint of further decreased vision and more pronounced reading
difficulties. Best-corrected visual acuities were unchanged as was preliminary testing, save strong tritanomalous color vision defects bilaterally on Farnsworth D15 testing (Figure 6) [Farnsworth D15 Color Test; Bernell, Mishawaka, IN].

Follow up 10-2 HVF demonstrated progressive centrocecal scotomas worsening in both depth and extent bilaterally (Figure 7).
As a progressive optic neuropathy with striking symmetry in the setting of a remote trauma would be unlikely, further investigation was initiated. A whole blood sample was collected and sequencing of the OPA1 and OPA3 genes was performed with copy-number variants detection [Prevention Genetics; Marshfield, WI]. The patient was found to be heterozygous in the OPA1 gene for a variant designated c.1834C>T, which is predicted to result in premature protein termination.

The diagnosis was subsequently revised to DOA with referrals generated to audiology, neurology, and genetic counseling.

The audiology consult returned with high frequency sensorineural hearing loss bilaterally (Figure 8) [Quasar Audiogram Module; Department of Veterans Affairs Health Systems Design & Development; Washington DC]. Longitudinal management was scheduled with the audiologist.

The neurology consult reported a constellation of symptoms including claudication of peripheral musculature with minimal exertion, peripheral neuropathy, episodic ataxia, resting tremors of hands, and a cogwheel-like kinetic tremor most notable in the forearms bilaterally (see associated video). The neurologic diagnosis was updated from medication-induced tremors to OPA plus syndrome.

Genetic counseling resulted in an extensive review of the patient’s pedigree spanning three generations without findings of vision loss, hearing loss, or neuromuscular abnormalities. Genetic testing of the three offspring was arranged.
The patient has been placed on a six month follow up regimen to monitor for progression of the optic neuropathy or the development of chronic progressive external ophthalmoplegia.

**Discussion**

DOA is the result of mutations within the OPA1 gene located at chromosome 3Q28-q29 and rarely within the OPA3 gene located at chromosome 19Q13. Both are encoded at the nuclear level but translate to a dynamin-related GTPase that is critical to mitochondrial inner membrane biogenesis, stabilization, and function. Loss of function induces mitochondrial dysfunction leading to an increase in reactive oxygen species and altered calcium homeostasis. The subsequent haploinsufficiency leads to premature apoptosis of neuronal tissue which has a predilection for the papillomacular bundle. Over time, the condition may progress to involve extra-ocular systems exposing the OPA plus phenotype.

Deletion, insertion, nonsense, missense, splicing, and truncative mutations in the OPA1 gene have been demonstrated with phenotypic variations ascribed to each. The variant in our patient was predictive of a premature termination of the OPA1 product which has been predicted to retain some GTPase activity and exert a dominant negative effect. This retained function could explain the lack of a discernable pedigree in this case.

DOA is inherited in an autosomal dominant fashion with a penetrance of 57% but widely variable phenotypic presentation. Symptoms of slowly decreased vision most often present in the first to second decades and stabilize in the third to fourth decade with more than 80% of patients retaining 20/200 or better Snellen acuity. Striking, bilateral, symmetric optic disc pallor and centrocecal visual field defects are a hallmark of DOA, while tritanopic color vision defects are common.

Progression to the plus phenotype signals a more guarded visual prognosis as visual acuity may continue to deteriorate into the fifth and sixth decades. We would suggest the lack of DOA pedigree and a sudden awareness of insidious vision loss following a blast exposure both delayed and confounded the diagnosis in this case.

Twenty percent of DOA patients will progress to a plus syndrome which may include neurosensory hearing loss, chronic progressive external ophthalmoplegia, myopathy, peripheral neuropathy, multiple sclerosis-like illness, or spastic paraplegia. Our case demonstrates late-onset high frequency hearing loss and a mitochondrial myopathy consistent with DOA plus syndrome.
Presently, there is no prophylactic or therapeutic measures for DOA. There have been several small-scale studies for potential supplemental therapy with mixed/anecdotal results. Patients may benefit from genetic counseling and low vision consultation when appropriate. Ethanol and tobacco products should be avoided as they may compound mitochondrial dysfunction.

Conclusions

DOA is the most clinically encountered hereditary optic neuropathy. While genetic analysis is definitive, early onset, characteristic optic disc pallor, centrocecal defects, tritanopia, and a consistent pedigree should raise suspicion for DOA. As the number of individuals progressing to DOA plus syndrome is not insignificant, we would suggest consultation with neurology and audiology is warranted in all cases. Similarly, genetic counseling and low vision therapies may be indicated. Longitudinal management is suggested as many phenotypes will progress later in life.

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