References


Footnotes and Disclosure

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Delayed diagnosis of autosomal dominant optic atrophy until seventh decade of life

Autosomal dominant optic atrophy (ADOA) is the most common hereditary optic neuropathy, manifesting in approximately 1 in 50,000 people, and up to 1 in 10,000 in Denmark, owing to a founder mutation. Isolated ADOA approximately 1 in 50,000 people, and up to 1 in 10,000 in common hereditary optic neuropathy, manifesting in the seventh decade of life.

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Patient 1, a 64-year-old Caucasian man, was referred to the neuro-ophthalmology clinic with a 12-year history of isolated, unexplained bilateral painless progressive central vision loss. His past medical history was significant for type II diabetes mellitus, hyperlipidemia, obesity, obstructive sleep apnea, and ocular hypertension. His regular medications were aspirin, atorvastatin, fenofibrate, metformin, montelukast, omeprazole, latanoprost, and sertraline. He did not smoke cigarettes or drink alcohol and reported a balanced diet. His family history was significant for an 11-year-old granddaughter who had recently been diagnosed with optic nerve hypoplasia.

The patient initially presented with painless bilateral slowly progressive vision loss 12 years prior. An initial diagnosis of cataracts was made with visual acuity of 20/100 OD and 20/80 OS and an otherwise normal eye examination. He underwent bilateral cataract extraction and intraocular lens implantation without improvement. Subsequent evaluation revealed an elevated intraocular pressure of up to 25 mm Hg, gonioscopy showing Shaffer grade 4 open angles, a cup-to-disc ratio of 0.3, and otherwise normal optic discs OU. He was treated with latanoprost for presumed glaucoma. In total, he saw 4 different ophthalmologists over 12 years. Optic atrophy was noted only in the records, 10 years after symptom onset, but it is likely that this ophthalmoscopic finding was present earlier in the course. The patient was referred to neuro-ophthalmology 12 years after initial presentation because the optic disc did not appear to be typically glaucomatous and because of central vision loss.

On neuro-ophthalmologic examination, the patient’s visual acuity was 20/40 OU. His pupils were isocoric without a relative afferent pupillary defect. Colour vision on Ishihara testing was 14/14 OU. Intraocular pressures were 17 mm Hg OD and 19 mm Hg OS. Dilated fundus examination showed optic disc pallor temporally OU, with a cup-to-disc ratio of 0.5 OD and 0.4 OS. The remainder of the eye and neurologic examinations was normal. Automated perimetry (Humphrey visual field 24-2) showed an enlarged blind spot and superior paracentral visual field defect, with a mean deviation of –3.55 dB OS, and a temporal visual field defect superiorly, with a mean deviation of –3.53 dB OD. Optical coherence tomography (OCT) showed average retinal nerve fibre layer (RNFL) of 64 µm OD and 65 µm OS, with primarily papillomacular bundle loss OU (Fig. 1). The OCT macular ganglion cell layer showed diffuse thinning.

The work-up for optic atrophy included magnetic resonance imaging of the brain and orbits with contrast material and was unremarkable. Laboratory studies, including complete blood count; determinations of sedimentation rate and C-reactive protein, folate, and angiotensin-converting enzyme levels; syphilis serology; and myelin oligodendrocyte glycoprotein testing, were unremarkable. Serum homocysteine was elevated at 14.9 µmol/L (normal <11.4 µmol/L), and the patient’s B12 level was low normal at 366 pg/mL (normal, 200–1100 pg/mL). Genetic testing revealed a pathogenic heterozygous frameshift mutation in the OPA1 gene, with a c.2708_2711:4 base pair deletion at codons 903–904. The diagnosis of ADOA was made, and the patient’s granddaughter with previously known optic nerve head abnormalities was also confirmed to have the same genetic diagnosis. Further family genetic counselling was recommended.

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Patient 2, a 63-year-old Caucasian woman, presented to the neuro-ophthalmology clinic with a 10-year history of painless progressive vision loss OU and a diagnosis of idiopathic optic atrophy. Her past medical history was significant for hypothyroidism, hyperlipidemia, and excision of a T7 World Health Organization grade 1 spinal meningioma. Her regular medications included levothyroxine and rosuvastatin. Her family history was significant for a recent diagnosis of idiopathic optic atrophy in her daughter. When the patient initially presented 10 years prior, the neuro-ophthalmic evaluation was significant for bilateral optic atrophy and bilateral epiretinal membranes. External investigations were performed with magnetic resonance imaging of the brain and orbits with contrast material; complete blood count; determinations of serum vitamin B₁₂, folate, and antinuclear antibodies; chest x-ray; and determinations of Fig. 1—Findings from patient 1 in the right eye (OD) and the left eye (OS) showing a paracentral scotoma on automated perimetry. Macular ganglion cell layer in both eyes shows diffuse thinning, with thinning of the retinal nerve fibre layer temporally at the optic disc in both eyes.
anti–aquaporin 4 antibodies and myelin oligodendrocyte glycoprotein antibodies returning negative. A multifocal electroretinogram was within normal limits in the setting of the known epiretinal membranes. The patient presented to a second neuro-ophthalmologist for further evaluation.

On examination, the patient’s visual acuity was 20/40 OD and 20/30 OS. Her pupils were isocoric without a relative afferent pupillary defect. Intraocular pressures were normal. Slit-lamp examination was significant only for mild nuclear sclerotic cataracts OU. Colour vision was 1/14 on the Ishihara test OU. Dilated fundus examination showed optic disc pallor temporally OU, with a cup-to-disc ratio of 0.4 OU. The remainder of her eye and neurologic examination was normal. Humphrey visual field 24-2 showed non-specific abnormalities OU, with a mean deviation of $-4.52\mu \text{dB OD and } -3.32\mu \text{dB OS}$. OCT showed a reduced average retinal nerve fibre layer thickness of 71\mu m OD and 58\mu m OS, with primarily papillomacular bundle loss OU. OCT of the macula showed bilateral epiretinal membranes with intraretinal cysts OD and average macula thickness of 415\mu m OD and 253\mu m OS (Fig. 2). OPA1 testing was performed and revealed a pathogenic heterozygous frameshift mutation, a c.2708_2711:4 base pair deletion at codons 903–904. The diagnosis of ADOA was confirmed, and recommendations were made for the patient’s family members to also undergo testing for the OPA1 mutation.

The typical age of presentation with reduced visual acuity in ADOA is commonly reported as being in the first 2 decades of life, with large studies across the world reporting ages between 4 and 10 years and a large meta-analysis reporting that 85% of patients with ADOA had symptom onset at <20 years of age. However, variable expressivity is well reported in the literature and identified commonly in mutation screening of affected family members—23% of patients in a report of 30 patients did not have clinical optic atrophy even when examined with a known diagnosis. Another report of ADOA patients noted that 27% of patients had no symptoms, and 10% had no abnormal clinical examination findings, highlighting variable expressivity.

Whether the age of onset of clinical symptoms affects the level of visual function is also not clearly known. In part, the possibility of patients with gradual vision loss not recognizing the symptoms until they are more severe and therefore having a delayed presentation or never presenting to medical attention could be a consideration. Further, it is suggested that deletions, nonsense, and splice-site mutations may offer a better visual outcome than missense mutations, and both our patients had the same deletion mutation. However, severe visual symptoms have been reported with older age at presentation—1 patient with ADOA plus (a proband in her family) had visual symptoms first in her 40s and was legally blind in her 70s.

Longitudinal studies looking at visual progression do not typically report findings of asymptomatic patients as much as they do symptomatic patients, but one such study of ADOA reported that 11 of 69 patients were identified with OPA1 mutations who reported being asymptomatic—although their ages were not recorded in the published results, the mean best-corrected visual acuity reported was 6/5.7 (20/19). Older patients (>40 years old with a mean age of 59.4 years) in this study (both symptomatic and asymptomatic) were noted overall to have a worse visual acuity of 6/23.3 versus 6/12.9 in patients under age 40 years, although the age of onset of disease in these patients is unclear. Another reported Australian family noted that 6 of the 8 family members manifested only visual symptoms in their fourth to fifth decades of life, again highlighting the variability in age of clinical presentation of OPA1 mutation.

The oldest reported age at diagnosis of ADOA was 62 years in a woman who also underwent multiple investigations and treatments, including a temporal artery biopsy and intravenous steroids, although this patient had a number of atypical features, including rapid-onset unilateral vision loss and optic disc edema, with a contralateral episode 9 months later. In a study looking at affected OPA1 mutation patients and mutation-free family members, there was a significant thinning of both the RNFL and the ganglion cell layer in affected patients, which was noted even in the youngest patient (8 years of age), suggesting that the structural deficit occurs at a young age. Other studies have noted that thinning of the RNFL over time is similar in patients with OPA1 mutations and control patients, although the absolute RNFL thickness is less in OPA1 mutation patients, also suggesting early onset of structural abnormalities in these patients. Specific OCT analysis in asymptomatic populations has not been well reported.

In summary, we describe 2 patients with a delayed diagnosis of ADOA, both aged in their 60s, who were probands for their families and led to diagnoses in their younger family members. Both our patients, in retrospect, had many features that made the diagnosis of hereditary optic neuropathy much more likely, including family histories of vision loss in younger generations, loss of visual acuity, temporal pallor on fundus examination, and papillomacular bundle loss on OCT, and 1 patient also had significant colour vision abnormalities. In both cases, however, our patients became the proband diagnosis for OPA1 mutation, and it was their positive result that led to recommendations for testing in other family members with visual symptoms. Both our patients underwent multiple investigations and treatment trials, including cataract surgery, prior to the diagnosis.

Clinicians should be aware of the possibility of ADOA as a clinically manifest disease in later life, prompting appropriate molecular diagnosis and possible genetic counselling in an otherwise untreatable condition.
Fig. 2—Findings from patient 2 in the right eye (OD) and the left eye (OS) showing nonspecific defects on Humphrey visual fields. Optical coherence tomography (OCT) of the macula shows bilateral epiretinal membranes with intraretinal cysts OD. OCT of the optic nerve shows bilateral retinal nerve fibre layer thinning, most significant in the papillomacular bundle.

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References
Intravenous tocilizumab in the treatment of resistant optic perineuritis

Optic perineuritis (OPN) is a rare orbital inflammatory disease that mainly involves the optic nerve sheath and surrounding tissues. It is accompanied by eye pain and various levels of optic nerve dysfunction, such as decreased vision, visual field defect, and positive afferent pupillary defect. In contrast to optic neuritis, OPN is not a self-limited disease and always requires treatment.1

The main treatment for OPN is systemic corticosteroid therapy, which causes rapid and dramatic improvement, but recurrence is common and requires a longer course of treatment.1 Nonsteroidal anti-inflammatory drugs (NSAIDs) and azathioprine, along with oral corticosteroids, have also been employed in the treatment of patients with OPN, but their effectiveness has not been consistent. The most resistant cases require radiation therapy.1

To the best of our knowledge, a steroid-free immunomodulatory therapy regimen has not been employed in the treatment of primary OPN. In the case reported here, for the first time we successfully employed tocilizumab for a patient with resistant primary OPN.

This study was approved by the New England Institutional Review Board, which has issued a waiver of informed consent for the retrospective chart review analysis. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. The participant provided consent for any identifying information for publication.

A 21-year-old man was referred to our centre for a second opinion on retrobulbar pain in his right eye that had started 1 year before presentation to us. The pain had been progressively worsening since it first started. Initial blood work-up for inflammatory diseases had been negative. Brain and orbital magnetic resonance imaging (MRI) with contrast medium early in the course of the disease had revealed enhancement of the optic nerve sheath near the right globe. Extensive blood work-up such as aquaporin-4 antibody, myelin oligodendrocyte glycoprotein antibody, and plasmablast panel also was negative or normal. Chest computed tomography scan was normal. Visual acuity, B-scan ultrasound, and visual fields of both eyes had been reported normal. The patient had deferred lumbar puncture.

The patient had been started on prednisone 20 mg/day with significant improvement in his symptoms. Five

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