Case Report

Autosomal Dominant Optic Atrophy Plus Syndrome: A Case Report

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Abstract

A 9-year-old boy of Indian origin presented with defective vision and nystagmus. The parents also complained of hearing loss. On examination he had bilateral optic atrophy. The condition was running in family with his mother and uncle having similar visual and hearing disturbances, clinodactyly and intellectual disability at later age. Targeted gene sequencing revealed one copy of c.1058G>T (p.S3531) variant of unknown significance in exon 11 of OPA1 gene that was pathogenic of Autosomal Dominant Optic atrophy plus syndrome. This case highlights the clinical spectrum associated with OPA1 mutations.

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Keywords: *Optic atrophy, hearing loss, OPA1 mutations.*

Introduction

Autosomal dominant optic atrophy plus syndrome is a neuro-ophthalmic condition characterised by bilateral degeneration of optic nerves, causing insidious visual loss, typically starting in first decade of life. The disease affects primarily the retinal ganglion cells and their axons forming the optic nerve. 80-99% of these patients have variable visual acuity ranging from normal to legal blindness associated with sensorineural hearing loss. About 20% of patients harbour extraocular multisystem features like myopathy, peripheral neuropathy, reduced tendon reflexes and abnormal colour vision. Molecular diagnosis is provided by the identification of a mutation in the OPA1 gene in its pathogenesis.

Case history

A 9-year-old boy of Indian origin presented along with his parents with complaints of gradual diminution of vision in both eyes since 5 years associated with hearing loss. He was elder of the two siblings born out of a non-consanguineous marriage. His younger brother was 3-year-old and had no complaints. His mother also had visual complaints, hearing loss, clinodactyly started in the first decade of life. Her intellectual development was normal. His uncle on the other hand had developed diminution of vision, profound hearing loss, clinodactyly in toddlerhood itself. Uncle had intellectual disability hence couldn't complete his education. On examination, patient had a best corrected snellen visual acuity of 6/60 in right eye and 4/60 in left eye for distance. Near vision was N18 in right eye and N24 in left eye with Roman near vision chart. Nystagmus was noted. Anterior segment examination was normal. Fundus examination showed bilateral optic atrophy (Figure 1). Colour vison was abnormal in both eyes (3/21 from Ishihara's colour plates). Visual fields and Optical coherence tomography for retinal nerve fibre layer (OCT-RNFL) was attempted but inconclusive due to nystagmus and poor fixation. On systemic evaluation, child had profound sensorineural hearing loss in both ears. Pure tone audiometry result showed threshold shift from normal limits in both ears suggestive of abnormal oto- acoustic emissions and non-functional cochlear outer

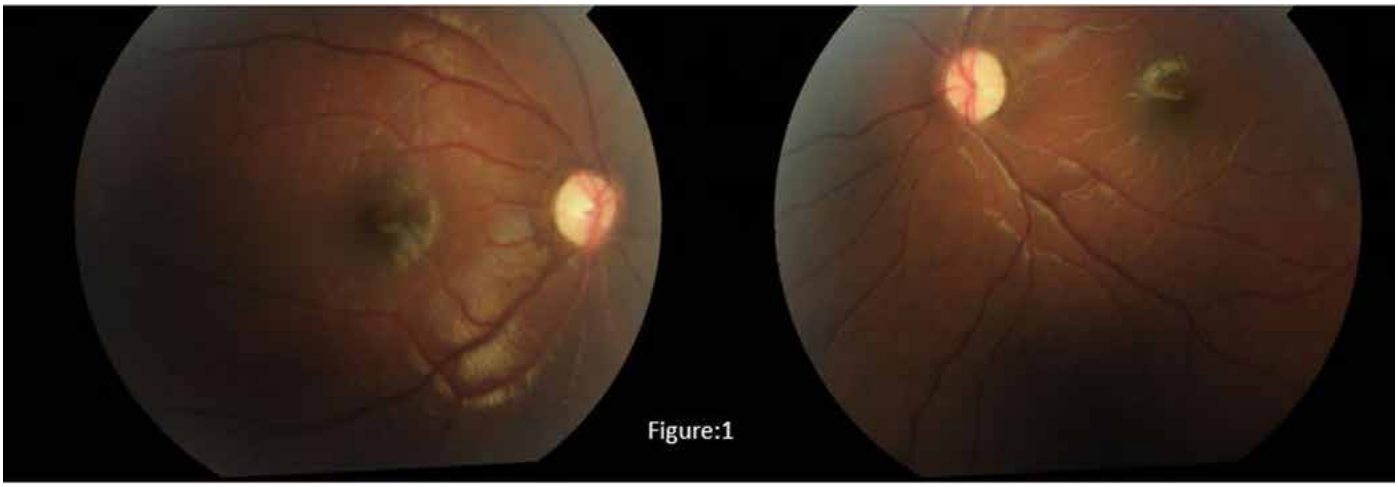

Figure 1: *Fundus photo of patient showing bilateral optic atrophy*

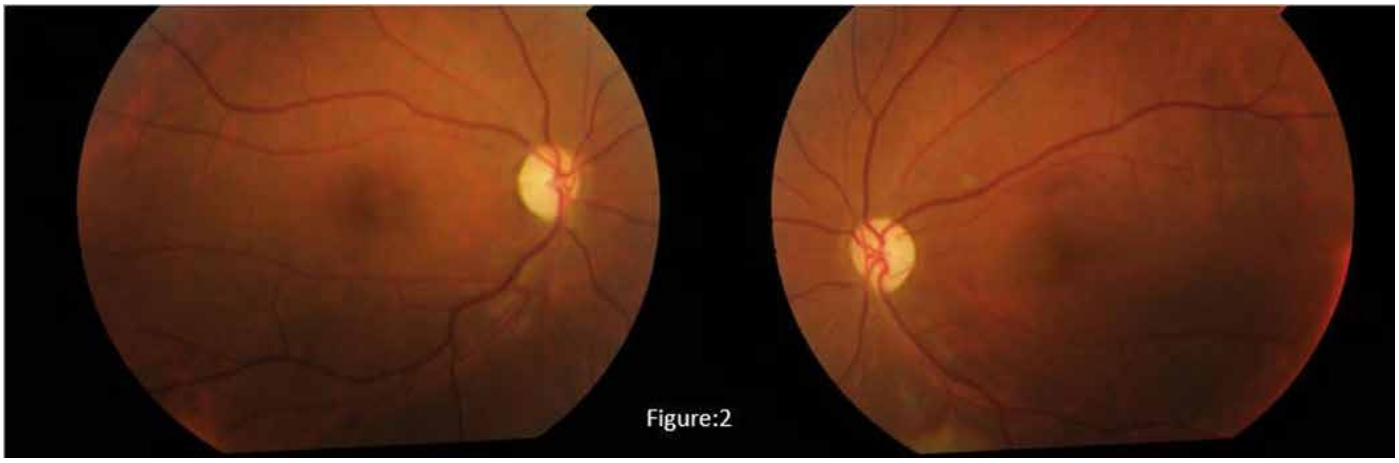

Figure 2: *Fundus photo of patient's mother showing bilateral optic atrophy*

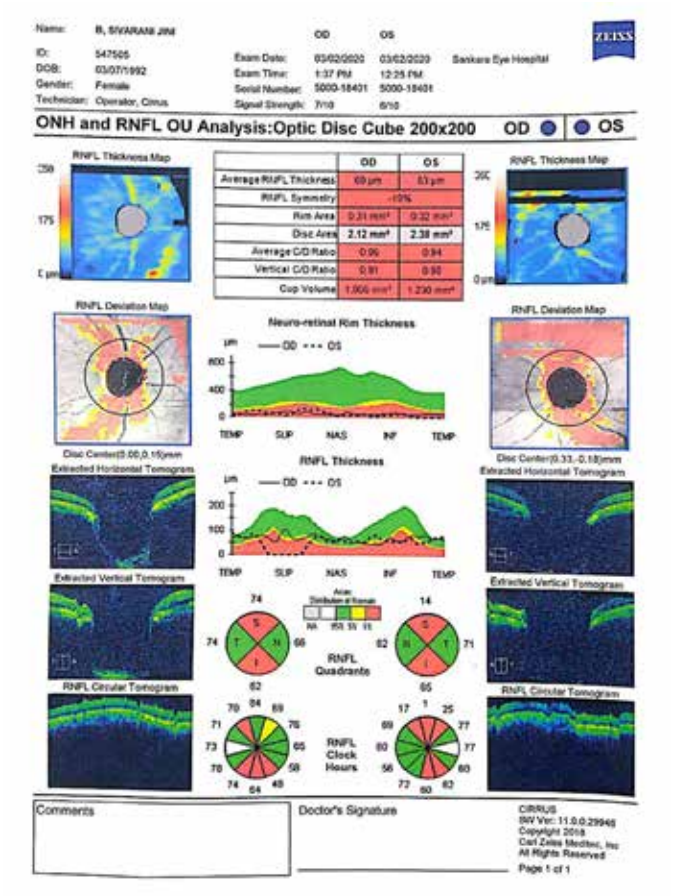

Figure 3: *OCT-RNFL of patient's mother*

hair cells. Mother on examination was also found to have bilateral optic atrophy (Figure 2) and similar audiometry results. Her right eye OCT-RNFL showed bipolar thinning and retinal nerve fibre layer loss but left eye OCT -RNFL was not reliable due to motion artifacts (Figure 3). Visual fields of the mother were also not reliable due to high false negatives (Figure 4). Examination of the younger sibling was normal. Since the family history was positive (Figure 5), targeted gene sequencing was performed which revealed a heterozygous missense variation in exon 11 of the OPA1 gene (chr3:193355763G>T; p.Ser353lle). This OPA1 gene variation is pathognomic of Autosomal dominant optic atrophy plus syndrome. Family segregation analysis
showed that the child and his mother were carrying the same mutation. His younger brother was not having the mutation. Hence the diagnosis of Autosomal dominant optic atrophy plus syndrome was confirmed. The patient was given low vision aid (LVA) trial which improved his near vision to N10 in both eyes (Roman near vision chart) and parents were counselled for LVA but they didn't opt for it. Patient has been advised regular follow up for ophthalmic examination. Hearing aid trial was given with digital hearing aid. Speech understanding was improved with hearing aid fitting along with the help of visual cues.

Discussion

Autosomal dominant optic atrophy plus syndrome (ADOA) is an autosomal dominantly inherited optic neuropathy due to the degeneration of optic nerve fibres and characterized by subnormal visual acuity and optic nerve pallor in the setting of an otherwise normal eye exam. Family history is often positive, but because of variable expressivity mildly affected family members may go undiagnosed (incomplete penetrance) Vision loss typically begins as the affected individual reaches school age. The onset and progression are insidious – most patients are unable to identify a precise age of onset. As many as 50% of patients with Autosomal Dominant Optic Atrophy plus syndrome experience a progressive loss of vision with advancing age. Dyschromatopsia (colour blindness) is frequently present but its manifestations are variable. Hearing loss that is caused by damage to the nerves of the inner ear (sensorineural hearing loss) typically develops during adolescence or young adulthood. Other symptoms of ADOA plus may develop in adulthood and include muscle weakness (myopathy), weakness of the eye muscles (ophthalmoplegia), trouble coordinating movements (ataxia), and pain and tingling in the arms and legs (peripheral neuropathy)The vast majority of Autosomal Dominant Optic Atrophy plus cases are caused by mutations in the gene OPA1, located on chromosome 3q. OPA1 is most

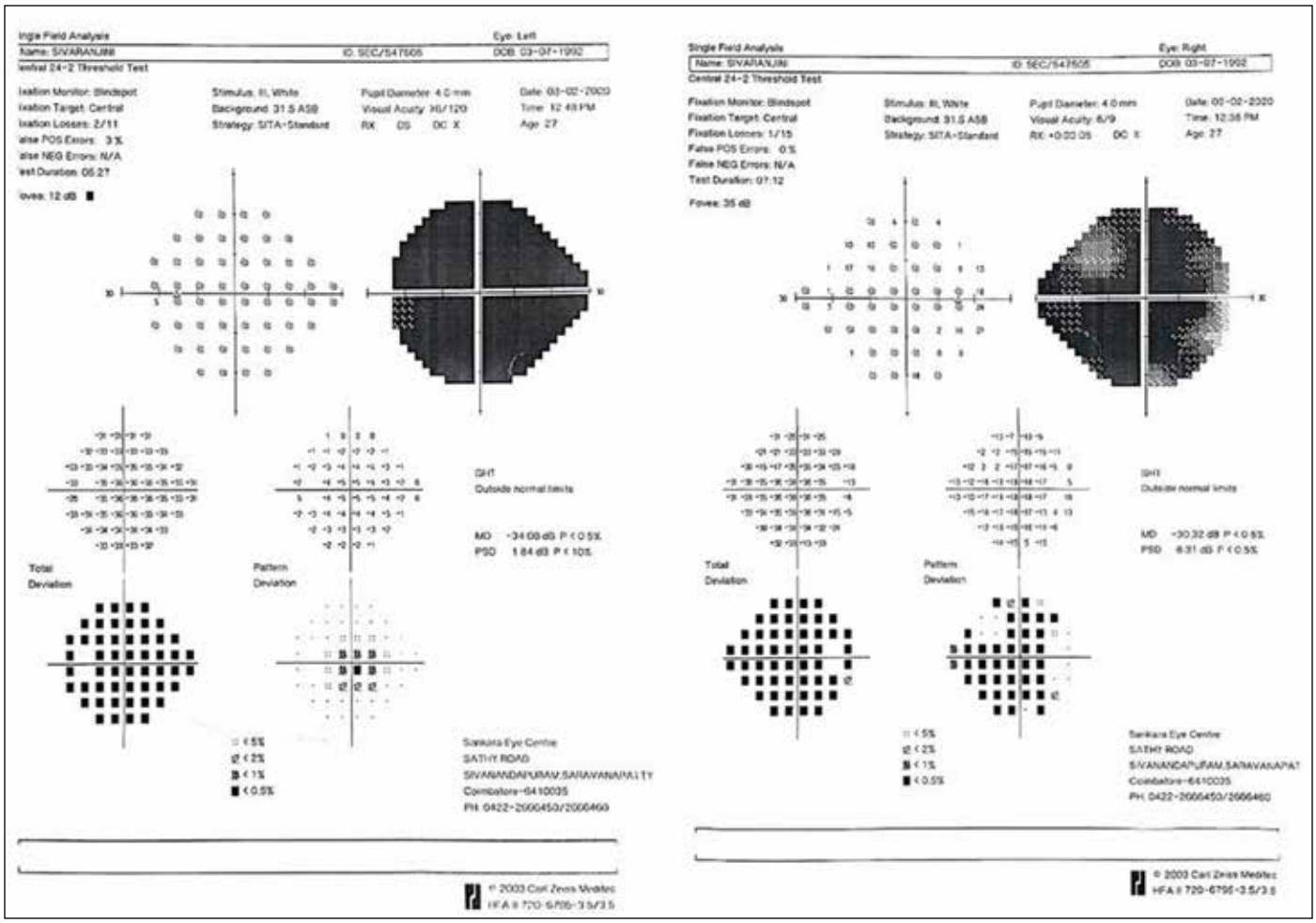

Figure 4: *Visual fields of patient's mother*

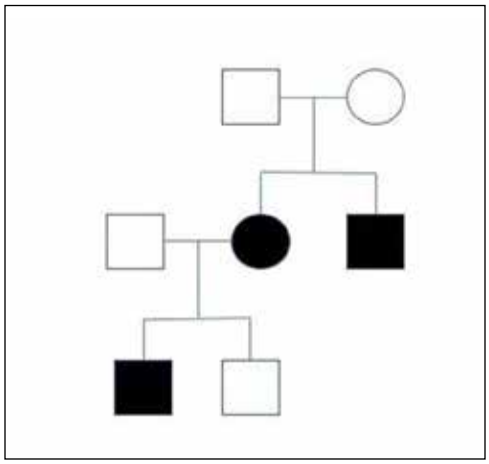

Figure 5: *Pedigree chart showing similar clinical manifestations in the family*

abundantly expressed in the retina and brain. The first ADOA locus, OPA1, localised on 3q28 was initially considered as unique.[1] But since the discovery of the OPA1 gene in 2000[2] two other loci, OPA4 and OPA5, were further identified in few families (1 for OPA4 and 2 for OPA5) presenting pure Dominant optic atrophy[3]. Additional loci and genes were identified as responsible for Optic Atrophy, but either with a X-linked mode of inheritance (OPA2)[4] a recessive mode of inheritance (OPA6 and OPA7)[5] or as syndromic recessive or dominant forms (OPA3 and OPA8). Thus, to date, OPA1 is the major gene responsible for ADOA, accounting for at least 75% of all the patients, whereas all the other genes or loci only contribute each for less than 1% of the patient cohort.

The management of ADOA patient consists in regular ophthalmologic examination, including measurement of visual acuity and colour vision. To date, no specific treatment exists, but low-vision aids in patients with severely decreased visual acuity can be beneficial. Cochlear implants have been shown to restore a marked improved audition in patients with ADOA plus syndrome with sensorineural deafness.

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