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Case Report

Ophthalmology Section

Novel Pathognomonic Variant of Atypical Type IV Usher Syndrome with Retinitis Pigmentosa- A Case Report

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ABSTRACT

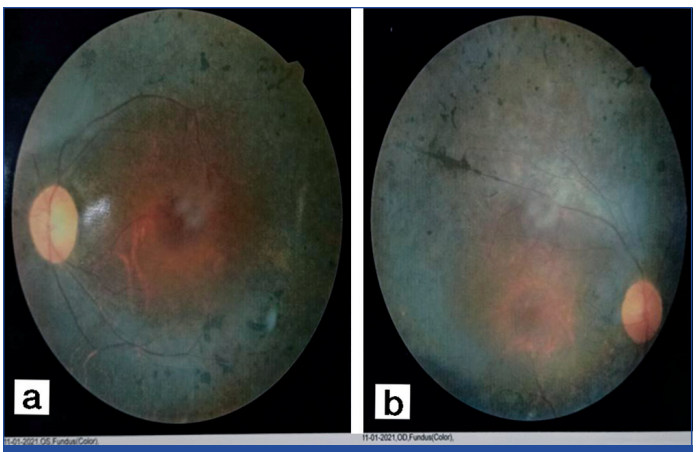
Retinitis Pigmentosa (RP) is a genetically heterogeneous group of inherited retinal disorders causing progressive dysfunction of rod photoreceptor and retinal pigment epithelium, may be seen in isolation or in association with systemic disease. This paper focuses on RP in an atypical type IV usher's patient. Usher's syndrome is a rare disorder and is the most common hereditary form of deaf-blindness. The management of these patients is multidisciplinary, involving specialists from different fields. Hereby, author present a case of 47-year-old male patient presented with chief complaints of defective vision in both eyes and defective vision in dim light for past six months. On fundus examination of both the eyes, he was diagnosed to have bilateral RP and on pure tone audiometry, he was diagnosed to have bilateral sensorineural deafness. Molecular gene analysis was done and it revealed *Arylsulfatase G (ARSG)* gene mutation. The patient was prescribed spectacles for his visual improvement.

Keywords: Pigmentary retinopathy, Phenotype, Sensorineural deafness

CASE REPORT

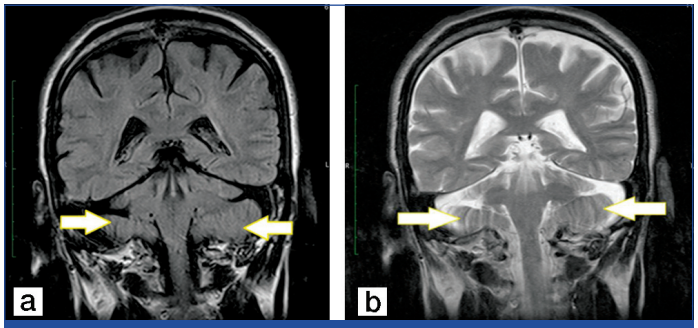
A 47-year-old male patient born out of non consanguineous marriage presented with history of blurring of vision in dim light for six months and defective vision in both eyes for two months. There was a past history of sensorineural deafness for 20 years and he was on hearing aid for the same. Patient gave history of cataract surgery done for both his eyes five years back and both eye Yttrium Aluminum Garnet (YAG) capsulotomy done two years back. There was no similar illness in family members and no other significant co-morbidities.

On ocular examination, his best corrected visual acuity in both eyes was 6/9 with Oculus dexter (OD)-1.00 Dsph and Oculus Sinister (OS)-0.50 Dsph. His near vision correction in both the eyes was +3.00 Dsph. On slit lamp examination, both eye anterior segments were normal, pseudophakic with posterior chamber intraocular lens in place with YAG capsulotomy opening present. On dilated fundus examination, with 90 D lens, waxy disc pallor, intra retinal mid peripheral bony spicules with arteriolar attenuation suggestive of Retinitis Pigmentosa (RP) were present in both eyes [Table/Fig-1a and b]. Macular function test by Amsler grid in both eye was normal. Dark adaptation test was prolonged in both eyes. Visual field by perimetry showed mid periphery visual field defects and full field electroretinography showed reduced b-wave with subnormal implicit time.



[Table/Fig-1a,b]: Showing the fundus picture of right eye and left eye with Retinitis Pigmentosa (RP).

Pure tone audiometry was done which showed bilateral moderate to severe sensorineural deafness. Magnetic Resonance Imaging (MRI) brain was done, which showed mild bilateral cerebellar atrophy with no other structural abnormalities [Table/Fig-2a and b].

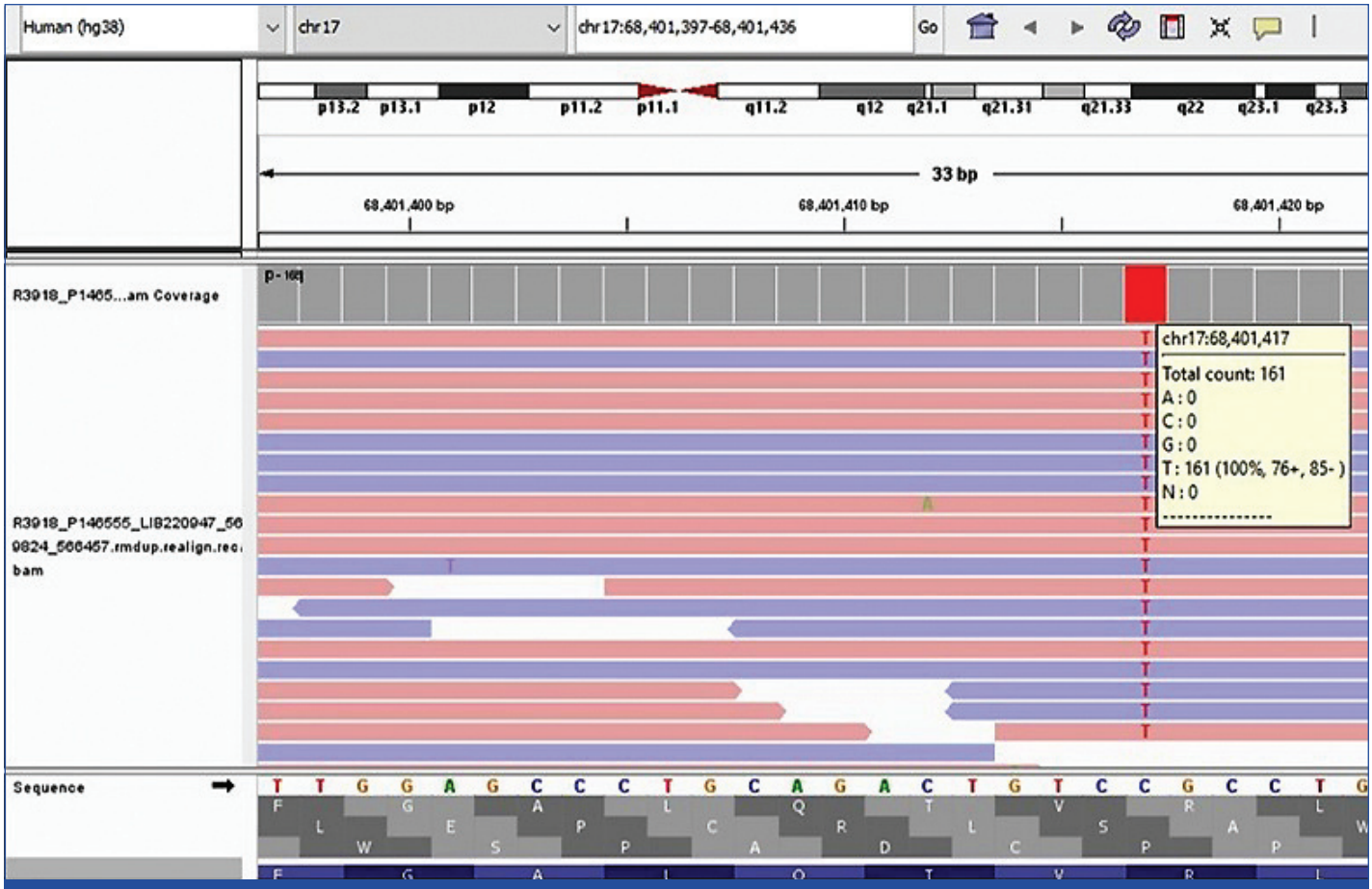


[Table/Fig-2]: a) T1W image; b) T2W image- Both images showing T1 and T2 weighted image of MRI brain coronal view with mild to moderate bilateral cerebellar atrophy with more marked on right side (arrow head).

Gene study with wide genome sequencing was done and it showed homozygous missense variation in exon 11 of the *ARSG* gene (amino acid substitution of cysteine for arginine at codon 424 p.Arg424cys) [Table/Fig-3]. Late adulthood onset sensorineural deafness without vestibular involvement with RP and *ARSG* gene mutation, confirmed the diagnosis of atypical form of Usher Syndrome (USH), here designated type IV. The patient was prescribed prophylactic antioxidant tablets like luetin, zeaxanthine for one month and spectacles according to his best corrected visual acuity. Visual prognosis was explained to the patient and he was advised follow-up every six months.

DISCUSSION

Usher syndrome is an autosomal recessive inheritance pattern and is characterised by the combination of Sensorineural Hearing Loss (SNHL), rod-cone dystrophy in the form of typical RP, and variable vestibular dysfunction [1]. Currently, it has three clinical subtypes and the most common ophthalmic manifestation of all three subtypes is the retinal degeneration, which is classified as rod-cone dystrophy or RP. Atypical USH has emerged to include USH phenotypes that do not meet the criteria for USH I, USH II, or USH III [1].



[Table/Fig-3]: Showing the genomic sequencing with *ARSG* gene mutation.

About 14% of all syndromic RP cases are associated with USH. RP belongs to group of pigmentary retinopathies with rod-cone dystrophy and pigment deposits in mid peripheral retina and relative sparing of central retina [1].

Diagnostic criteria of RP include night blindness (earliest symptom), loss of peripheral field of vision with ring shape scotoma and tunnel vision, bony spicules in mid periphery, attenuation of retinal vessels, waxy optic disc pallor and diminuation in b-wave amplitude in electroretinogram.

Khateb S et al., described five patients from three Yemenite Jewish families (*MOL0120, MOL0737, and TB55*) with an atypical form of USH. Over the time, pigment migration occurred within the atrophic areas, forming bone-spicule-like pigmentary changes as well as pigment clumps, and the central macula also became involved [2].

Abad-Morales V et al., reported a 44-year-old Spanish woman who presented at 40 years of age with progressive nyctalopia and a history of hearing loss since infancy. Ophthalmologic examination showed retinal epithelium pigment abnormality extending beyond the optic nerve with mid-peripheral spicule-like abnormalities [3].

Peter VG et al., reported two Portuguese women with USH type IV [4]. Fowler NH et al., reported a 60-year-old patient with a 20-year history of progressive SNHL and a 10-year history of progressive peripheral vision loss and pigmentary retinopathy. The patient was homozygous for the ARSG variant. On fundus examination, ring-shaped retinal hyperpigmentation was observed and six zone pattern of autofluorescence was noted on fundus autofluorescence [5].

Simultaneous occurrence of RP and deafness was first recognised by Von Grafe (1858), but the syndrome was termed after Usher in 1914 [1]. Usher's syndrome is a rare autosomal recessive inheritance disease and catogorised into three main types based on the clinical presentation and the gene mutation. *MYO7A* and *USH1C* gene mutation are seen with type 1 and *USH2A* and *CLRN1*, *USH3* gene mutation in type 2 and type 3 [6-9], respectively [Table/Fig-4]. It is characterised by progressive SNHL with and without vestibular dysfunction and RP. The prevalence of usher's syndrome is reported as 16.7 per 100,000 [10].

Type	Gene mutation	Clinical features
Type I	*MYO7A* USH 1C	Profound congenital hearing loss, Retinitis Pigmentosa (RP), Absent vestibular function
Type II	USH IIA	Moderate congenital hearing loss, RP, Normal vestibular function
Type III	*CLRN1*	Progressive hearing loss, Vestibular dysfunction, RP occurs in 2nd to 4th decade.

[Table/Fig-4]: Types of Usher's syndrome with clinical features [1].

More recently several genes associated with atypical USH have been proposed. These include *PDZD7, HARS, ABHD12, CIB2, CEP250, CEP78, ARSG [1], and ESPN.*

Atypical Ushers type IV is a rare variant of usher's syndrome associated with the mutation in *ARSG* gene and characterised by late adulthood onset of SNHL without vestibular dysfunction and RP [1]. It is quite evident from this case report that an array of findings can be seen in the patient.

CONCLUSION(S)

The approach to management of Usher's syndrome is multidisciplinary and symptomatic to a large extent. Establishing a criteria for diagnosis and characterisation of genetic causes will benefit the clinicians and scientist who are working to understand and treat this condition and also establish a common foundation on which future research can be built.

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