Original Article

Retinitis pigmentosa in Usher syndrome in India: Electronic medical records driven big data analytics: Report III

Deepika C Parameswarappa, Anthony Vipin Das[1]*, Mariya Bashir Doctor[2], Ramya Natarajan[3], Komal Agarwal, Subhadra Jalali*

Purpose: To describe the clinical presentation and demographic distribution of retinitis pigmentosa (RP) in patients with Usher syndrome (USH). **Methods:** This is a cross-sectional observational hospital-based study including patients presenting between March 2012 and October 2020. In total, 401 patients with a clinical diagnosis of USH and RP in at least one eye were included as cases. The data were retrieved from the electronic medical record database. For better analysis, all 401 patients were reclassified into three subtypes (type 1, type 2, and type 3) based on the USH criteria. **Results:** In total, there were 401 patients with USH and RP, with a hospital-based prevalence rate of 0.02% or 2/10,000 population. Further, 353/401 patients were subclassified, with 121 patients in type 1, 146 patients in type 2, and 86 patients in the type 3 USH group. The median age at presentation was 27 years (IQR: 17.5–38) years. There were 246 (61.35%) males and 155 (38.65%) females. Males were more commonly affected in all three subtypes. Defective night vision was the predominant presenting feature in all types of USH (type 1: 43 (35.54%), type 2: 68 (46.58%), and type 3: 40 (46.51%) followed by defective peripheral vision. Patients with type 2 USH had more eyes with severe visual impairment. **Conclusion:** RP in USH is commonly bilateral and predominantly affects males in all subtypes. Patients with USH and RP will have more affection of peripheral vision than central vision. The key message of our study is early visual and hearing rehabilitation in USH patients with prompt referral to otolaryngologists from ophthalmologists and vice versa.

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Usher syndrome (USH) is a genetic disorder characterized by a constellation of neurological, auditory, and ophthalmic features.[1] Previous studies on the western population have reported the prevalence of USH to be 1/10,000 to 1/50,000 people.[2,3] In high consanguineous areas like the middle east and India, the prevalence is not available for the larger population. USH is the most common prevalent cause of hereditary deafness and blindness.[3-6] It is a heterogenic autosomal recessive disorder with sensorineural hearing loss, vestibular disturbances, and pigmentary retinopathy such as retinitis pigmentosa (RP).[6] To date, mutations in around 10 genes have been reported as the causative factor for USH, some of the major genes being *MYO7A (USH1B), USH1C, CDH23, PCDH15 (USH1F), USH2A, and USH3A*.[7,8] As the inheritance pattern is autosomal recessive, higher chances of occurrence of disease with a history of consanguinity are noted.[9-11]

USH is subclassified into three types based on the onset and severity of hearing loss, vestibular disturbances, and RP. USH type 1 is characterized by congenital profound deafness, vestibular abnormalities, and RP within the first decade of life. Patients with type 2 USH show moderate to severe congenital hearing loss and no vestibular abnormalities and RP within the second decade of life. USH 3 is characterized by progressive and variable hearing loss, vestibular abnormalities, and RP.[6,12] RP and deafness at an early age lead to the loss of cognitive skills and affect psychosocial well-being.[13,14]

There is no definitive therapy for USH so far. Management is directed toward supportive therapy depending on the severity of deafness and RP. Early rehabilitation is the key in USH syndrome as hearing and vision are major concerns in cognitive development.[15] Patients with type 1 USH have good outcomes with cochlear implants for hearing.[16] Patients with type 2 and 3 USH are supported with hearing aids majorly.[1,17] As there is no definitive cure for RP, early visual rehabilitation and low vision aids are the mainstays for patients with USH.

Previous studies have assessed the genetic parameters, inheritance pattern, and clinical features of USH. However, large data set of USH from any hospital-based study is lacking. Herein we report the characteristics from a large data set of

Srimati Kanuri Santamma Centre for Vitreoretinal Diseases, [1]Department of EyeSmart EMR & Aeye, [2]Standard Charted Eye Care Education, [3]Department of Ophthalmic Biophysics, L V Prasad Eye Institute, Hyderabad, Telangana, India
*Denotes equal contribution

Correspondence to: Dr. Subhadra Jalali, Srimati Kanuri Santhamma Center for Vitreo Retinal Diseases, L V Prasad Eye Institute, Hyderabad, Telangana – 500 034, India. E-mail: subhadra@lvpei.org

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USH syndrome with RP presenting to a tertiary ophthalmic center in south India.

Methods

Study Design, Period, Location, and Approval: This cross-sectional observational hospital-based study included all patients presenting between March 2012 and October 2020 to an ophthalmology network located in 200 geographical locations spread across four states (Telangana, Andhra Pradesh, Odisha, and Karnataka) of India.[18] The patient or the parents or guardians of the patient filled out a standard consent form for electronic data privacy at the time of registration. None of the identifiable parameters of the patient information were used for the analysis of the data. The study adhered to the Declaration of Helsinki and was approved by the institutional ethics committee (Ethics Reference No. LEC-BHR-R-09-20-505).

The clinical data of each patient who underwent a comprehensive ophthalmic examination was entered into a browser-based electronic medical records system (eyeSmart EMR) by uniformly trained ophthalmic personnel and supervised by an ophthalmologist using a standardized template.[19]

Cases: A total of 2,541,810 patients of all ages presented to the tertiary and secondary centers of the network during the study period. The eyeSmart EMR was initially screened for patients with the final diagnosis of RP in one or both eyes with USH. The diagnosis was based on clinical examination by a trained ophthalmologist and review of EMR records by a fellowship-trained retina specialist. The diagnostic criteria used for RP were diffuse/or and widespread retinal pigment epithelial degeneration, arterial narrowing, disc pallor, commensurate visual field loss, and whenever available, reduced amplitudes on electroretinogram (ERG) with evidence of rod and cone involvement.[20] The clinical criteria used for USH were the presence of RP with at least one or both congenital or variably progressive sensorineural hearing loss and vestibular disturbances as per standard criteria.[1,6]

Data Retrieval and Processing: In total, 401 patients with RP and USH syndrome were included in this study out of 15,062 RP patients. The data were retrieved from the electronic medical record database and segregated in a single excel sheet. The columns included data on demographics, clinical presentation, and ocular diagnosis and were exported for analysis. For better analysis, all 401 patients were reclassified into three subtypes (type 1, type 2, and type 3) based on the USH criteria.[1,6]

Patients who could not be classified into any of the subtypes due to lack of proper delineation of the presenting features were labeled as unspecified group with USH. The excel sheet with the required data was then used for analysis by using the appropriate statistical software. Standardized definitions were used for geographic locations, occupations, and socioeconomic status.[21,22] The visual acuity was classified according to the WHO guidelines.[23]

Statistical Analysis: Descriptive statistics using mean ± standard deviation and median with inter-quartile range (IQR) were used to elucidate the demographic data. Chi-square test (Stata software, Stata Corp. 2015. College Station, TX: Stata Corp LP) was used for univariate analysis to detect significant differences in the distribution of demographic features between patients with RP and the overall population.

Results

Prevalence: Of the 2,541,810 patients who presented across the network during the study period, 401 patients were diagnosed with USH and RP in at least one eye, translating into a hospital-based prevalence rate of 0.02% or 2/10,000 population. The proportion of RP with USH was 2.6% (401 out of 15,062 total RP patients during the study period).

Subgroups of USH syndrome: Out of 401 RP patients with USH syndrome, 353 were subclassified, with 121 patients in the type 1 group, 146 patients in the type 2 group, and 86 patients in the type 3 group. The remaining patients (n = 48) were kept as unspecified as mentioned in the methodology.

Age: The mean age of the patients with USH and RP at presentation was 29 ± 15.17 years, while the median age was 27 years (IQR: 17.5–38) years. The majority among them were adults (309/401: 77.06%), and the minority were children (92/401: 22.94%). The majority among them were in the age group of 21–30 years (104/401, i.e., 25.94%). Further, 95/401 (23.69%) were in the age group of 11–20 years, 82/401 (20.45%) were in the age group of 31–40 years, and 33/401 (8.23%) patients were above 50 years of age [Fig. 1]. Type 1 USH with RP was seen in equal occurrence in adults and children (66;55), type 2 had the majority of patients presenting in adulthood (109/146 patients, i.e., 74.66%), and type 3 had no patients presenting during childhood. This indicates the appearance of RP and ocular symptoms earlier in type 1 compared to type 2, while type 3 mainly develops later in life.

Sex: There were 246 (61.35%) male and 155 (38.65%) female patients with RP and USH. Males were more commonly affected in all three types of USH, with the ratio of males to females being 77:44 in type 1, 88:58 in type 2, and 51:35 in type 3. The overall hospital-based prevalence of RP was significantly greater in males (0.02%; 246/1371479) as compared to females (0.01%; 155/1170331) ($P < 0.0001$).

Rural-Urban-Metropolitan Distribution: There were 209 (52.12%) patients of RP with USH from rural districts, 150 (37.41%) from urban districts, and 42 (10.47%) from metropolitan regions. The occurrence of RP was higher in the

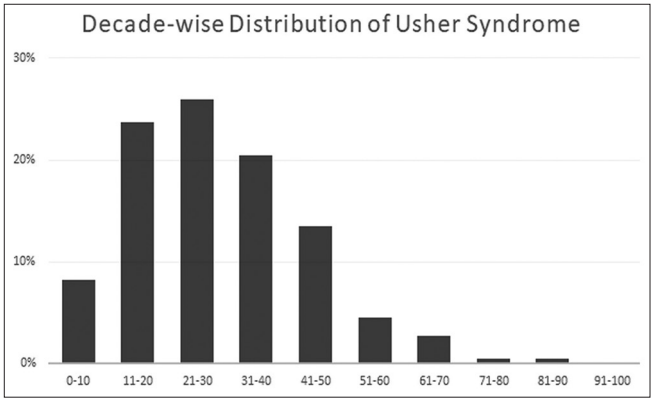

Figure 1: Bar graph showing the decade-wise distribution of Usher syndrome patients

rural community strata (0.02%, 209/1,143,643) as compared to urban community strata (0.01%, 150/1,097,863).

Socioeconomic Status: There were 140 (34.91%) patients with USH syndrome from the lower socioeconomic class, 249 (62.09%) from the lower-middle class, 10 (2.49%) from the upper-middle class, and 2 (0.50%) from the upper class. The overall prevalence of USH syndrome was significantly higher ($P < 0.00001$) in the lower socioeconomic strata (0.022%; 140/640,654) as compared to the higher socioeconomic strata (0.013%; 261/1,901,156).

Occupation: Of the 401 patients with RP and USH, 147 (36.66%) were students, 62 (15.46%) were professionals, 46 (11.47%) were homemakers, 26 (6.48%) were manual laborers, 34 (8.48%) were agriculturists, 5 (1.25%) were retired, and the occupational category was not available/applicable for the remaining 81 (20.19%). The overall prevalence of RP and USH in students (0.03%, 147/434,713) was significantly higher ($P < 0.00001$) in comparison to other professions. We do not have the data specific to educational status in specialized schools for all the patients. However, the data includes children with combined educational status from regular schools, integrated schools, and special need schools.

Presenting Complaints and Family History: Of the 401 patients with RP and USH, 154 (38.40%) complained of defective night vision, 29 (7.23%) had defective peripheral vision, 9 (2.24%) had photophobia/photopsia, and 3 (0.75%) patients complained of defective central vision. There was a family history of RP in 50 (12.47%) patients, 40 (9.98%) patients had a history of parental consanguineous marriage, and 11 (2.74%) patients had a history of both. Type 2 USH had more family history (23/50 patients with positive family history) and parental consanguinity when compared to type 1 and type 3. Defective night vision was the predominant presenting feature in all the types of USH (type 1: 43 (35.54%), type 2: 68 (46.58%), and type 3: 40 (46.51%), followed by defective peripheral vision.

Laterality and Ocular Comorbidities: RP in USH was bilateral in 387 (96.51%) cases. Further, 14/788 eyes did not have mention of RP such as fundus in the files: 3/14 eyes had normal fundus, and the remaining 11/14 eyes had absorbed old cataract, total corneal opacity, and occlusion pupillae, which obscured the view of the fundus. In the 788 eyes affected with RP with USH, associated cataract was found in 153 (19.42%) eyes, 37 (4.70%) were pseudophakic at presentation, 12 (1.52%) had glaucoma, 2 (0.25%) had coats disease, and 2 (0.25%) had retinal detachment. Coats' disease and retinal detachment cases were seen only in patients with USH type 1.

Best-Corrected Visual Acuity (BCVA): In the 788 eyes, mild or no visual acuity impairment (20/20–20/70) was seen in 341 (43.27%) eyes, moderate visual impairment (>20/70–20/200) in 127 (16.12%) eyes, severe visual impairment (>20/200–20/400) in 44 (5.58%) eyes, blindness 3 (>20/400–20/1200) in 135 (17.13%) eyes, and blindness 4 (>20/1200–PL) in 37 (4.70%) eyes. The visual acuity was undetermined or unspecified in 97 (12.31%) eyes. Patients with type 2 USH had more eyes with severe visual impairment (>20/200–20/400) and blindness 3 (>20/400–20/1200) compared to type 1 and type 3. Half of the patients with RP and USH syndrome (50.12%, i.e., 201/401) had visited our visual rehabilitation and low-vision aids center for services.

Spherical Equivalent: In the 788 eyes, emmetropia (−0.50 to +0.50D) was seen in 55 (6.98%) eyes, mild myopia (>−0.50 to −3.00D) in 123 (15.61%) eyes, moderate myopia (>−3.00 to −6.00D) in 72 (9.14%) eyes, high myopia (>−6.00D) in 48 (6.09%) eyes, mild hyperopia (>+0.50 to +3.00D) in 26 (3.30%) eyes, and moderate hyperopia (>+3.00 to +6.00D) in 9 (1.14%) eyes where refraction was performed at presentation. Overall, mild to moderate myopia was the predominant refractive error.

Lens: In the 788 eyes, the lens findings included nuclear cataract in 97 (12.31%) eyes, subcapsular cataract in 51 (6.47%), cortical cataract in 17 (2.16%) eyes, total cataract in 2 (0.25%), and complicated cataract in 6 (0.76%) eyes. Our data show that nuclear cataract was more common in the USH patients with RP.

Vitreous: In the 221/788 eyes, vitreous findings were available, and the findings included posterior vitreous detachment in 11 (1.40%) eyes and vitreous opacities in 19 (2.41%) eyes.

Macula: In the 788 eyes, the macular findings included foveal thinning in 57 (7.23%) eyes, epi-retinal membrane in 30 (3.81%), macular edema in 22 (2.79%) eyes, and macular hole in 3 (0.38%) eyes.

Retina: In the 788 eyes, the retinal signs included waxy disc pallor in 642 (81.47%) eyes, attenuated vessels in 675 (85.66%), and bony spicule pigmentation in 733 (93.02%) eyes. All eyes had diffuse or widespread retinal pigment epithelial degeneration signs [Figs. 2 and 3].

Surgical Management: A minor proportion required surgical intervention. The most common procedure performed was cataract surgery (33/788 eyes, 4.19%). Additionally, 21 eyes had already undergone cataract surgery before coming to us. One eye needed vitreoretinal surgery for rhegmatogenous retinal detachment. None of the patients had glaucoma procedures or intravitreal injections performed. In 11 patients, history of systemic surgeries was available, with 9 patients for cochlear implants and 2 patients for cardiac surgeries.

Discussion

Our study covers a large cohort of patients with 401 patients having RP in USH. The prevalence of USH was previously noted to be from 1/10,000 to 1/50,000 people. The hospital-based prevalence rate of RP with USH is 0.02% or 2/10,000 population as per our study. The prevalence was also noted to be higher in a rural community when compared to urban and metropolitan cities. This may be due to the higher occurrence of consanguineous marriages in rural communities in India.[9-11]

We further classified 353/401 patients into three subtypes (type 1, type 2, and type 3) based on the USH criteria. Type 1 and type 2 USH were more common than type 3 in our study. The majority of patients with RP and USH in our study were in the age group of 21–30 years. Appearance of RP, ocular symptoms, and presentation to the hospital was noted to be during adulthood in type 1 and type 2, whereas type 3 patients presented later in life, which is as expected based on the group definitions. However, a surprising finding noted was that early childhood presentation of type 1 patients into eye hospitals was less common. Because group 1 has congenital deafness, very often also associated with failure to

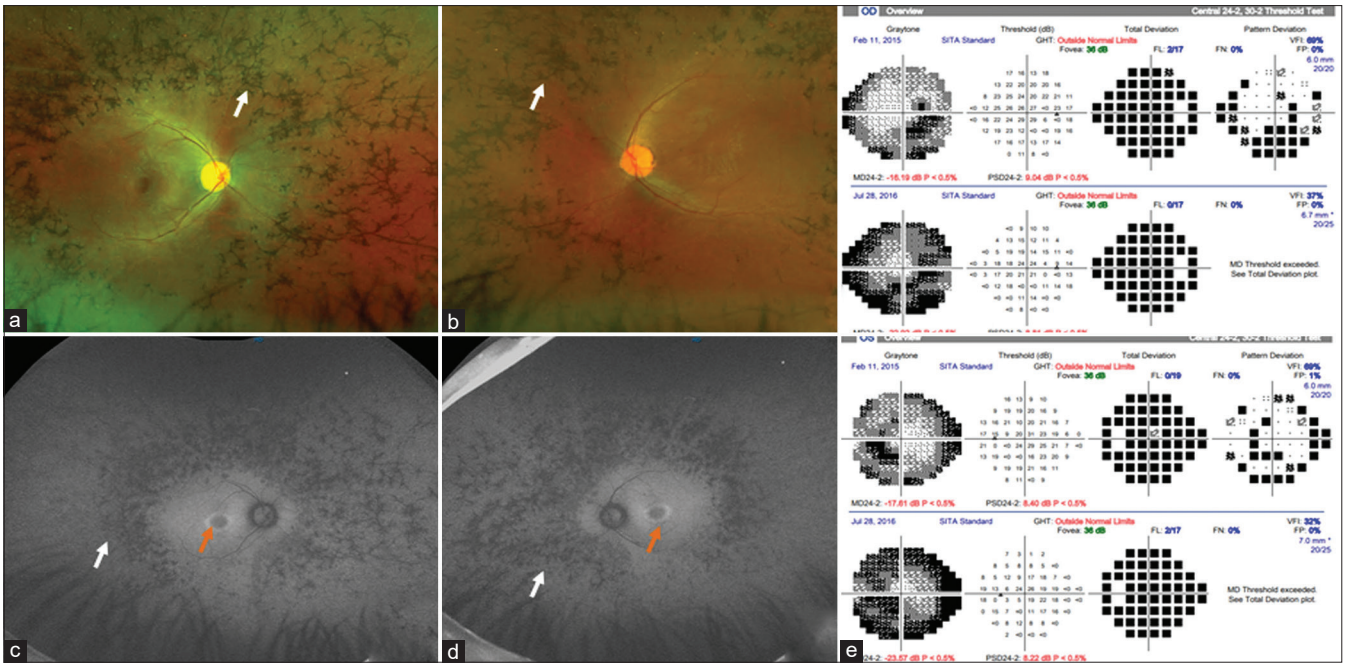

Figure 2: A 25-year-old male with Usher syndrome: Fundus photograph of both eyes (a and b: white arrows) showing bony spicule pigmentation and attenuated arteries. Fundus autofluorescence of both eyes (c and d) showing hypoautofluorescence corresponding to the pigmentary changes (white arrows) and parafoveal hyperautofluorescent ring (orange arrows). Humphrey visual field examination of both eyes showing affection of peripheral visual field and progression over a period of 1 year (e)

speak (deaf-mute), we would have expected that such children, even when asymptomatic, would have been screened for RP to rule out USH syndrome. However, at least in our communities, this did not seem a common practice. In fact, some patients had cochlear implants in childhood but no eye examination was conducted at that age or thereafter. Our clinical practice does not see deaf-mute children referred for retinal screening. This causes delayed vision rehabilitation. Also, due to a lack of information on the potential for vision loss that creeps in slowly, many children undergo lip-reading training only to lose this art later in life once vision starts to deteriorate. We suggest that clinics that conduct audiology on children or do cochlear implants must get retinal screening done as part of clinical workup.

Males were more commonly affected in all three types of USH. The prevalence of RP was higher in the rural community. This indicates possibly delayed loss of central vision in patients of RP and USH. Defective night vision was the predominant presenting feature in all types of USH, followed by defective peripheral vision. Prominent retinal feature in all eyes with USH was retinal pigment epithelium degeneration and atrophy, similar to other reports on USH retinal findings. Macular atrophy and cystoid macular edema are the most common macular features found in patients with RP and USH.[24,25] Foveal atrophy, epiretinal membrane, and macular edema were the most common macular features in our study. Abdelkader *et al*. had shown macular atrophy in most of their patients in a series of cases with type 1 USH and RP.[24] The most common ocular comorbidity found was cataract. Glaucoma, coats, and rhegmatogenous retinal detachment were among the rarer associations that we detected. Patients with type 2 USH had more eyes with severe visual impairment compared to type 1 and type 3. Previously, electrophysiological studies on patients with type 2 USH have reported the loss of central vision due to affection of cones by the second decade. The type 2 USH group in our study also showed similar affection of vision during the second decade; however, we do not have the electrophysiological analysis data for all patients to support the same. Galli-Resta *et al*. had performed focal macular ERG in patients with type 2 USH to assess the affection of cone function over a period of 22 years.[26] Visual acuity loss in type 3 USH is noted to be rapidly progressing compared to type 2 USH.[27] Progression of RP in USH was not assessed in our study as it is a cross-sectional study. Mild to moderate myopia was the predominant refractive error in the whole group as well as in subtypes.

The greatest strength of this study was the large sample size of USH with RP. The limitation of this study was its hospital-based method of data collection, which might have resulted in some ascertainment bias. Lack of ancillary investigations such as electrophysiology, OCT, fundus autofluorescence, and HVF assessment of retinal functions in all patients is one of the major limitations to correlate the vision affection in various types of USH as described in previous studies. Genetic testing or counseling could not be performed in all the cases due to a lack of patient awareness, acceptability, and accessibility to the services.

Conclusion

RP in USH syndrome is commonly bilateral and predominantly affects males in all types of USH syndrome. Patients present in the first to second decade of life in type 1 and type 2 USH. Type 3 USH will have presentation in later adulthood. The prevalence of RP with USH is higher in the rural community and is linked to a history of consanguinity. Patients with USH and RP will have more affection of peripheral vision, while

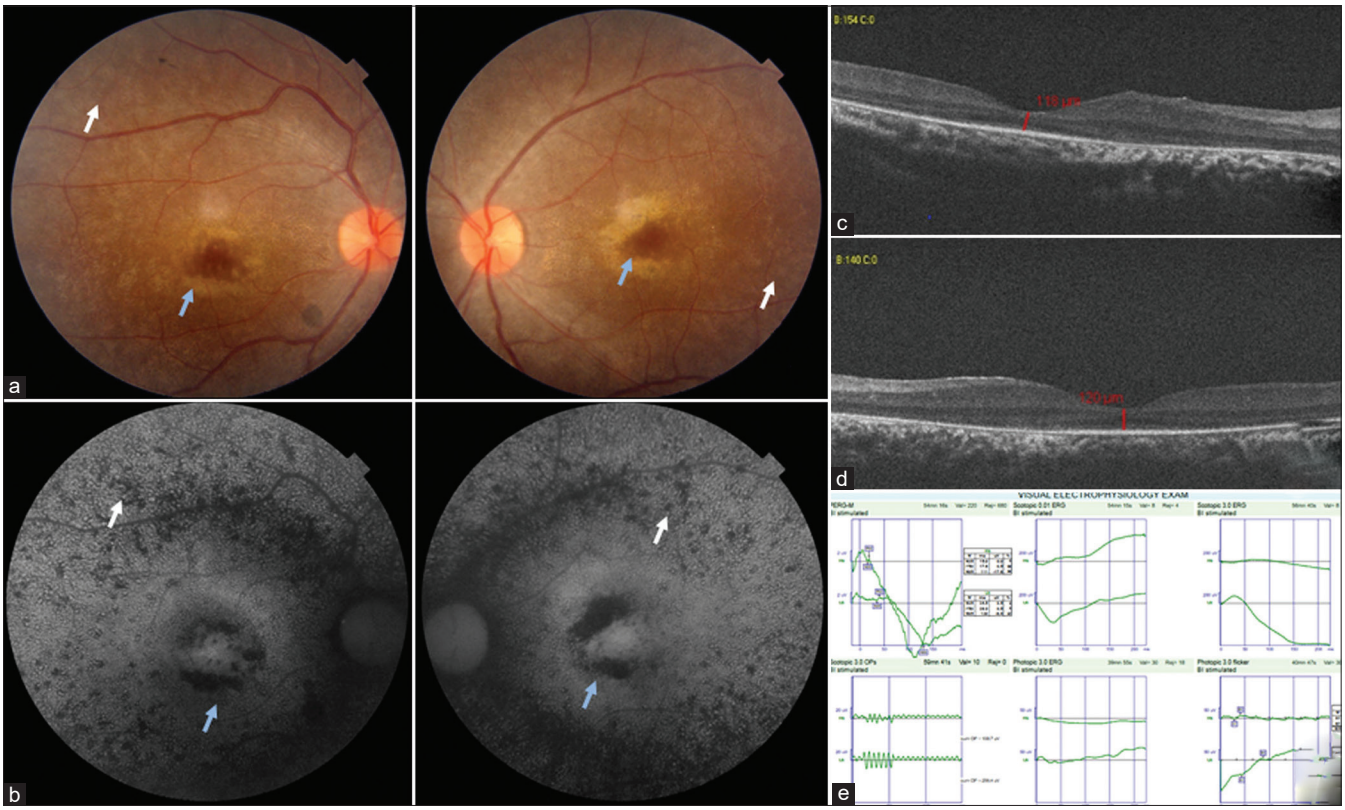

Figure 3: A 22-year-old female with Usher syndrome: Fundus photograph of both eyes (a) showing diffuse retinal pigment epithelial degeneration (white arrows) and parafoveal atrophic changes (blue arrows). Fundus autofluorescence of both eyes (b) showing hypoautofluorescence corresponding to the pigmentary changes (white arrows) and atrophy (blue arrows). Optical coherence tomography of the macula showing diffuse loss of photoreceptor layer in both eyes (c and d) and full-field electroretinogram showing reduced scotopic as well as photopic responses (e)

central vision is maintained till later part of life, similar to non-syndromic RP. Myopia is the predominant refractive error, and nuclear cataract is the common form of cataract seen in RP with USH. It is important to rule out USH syndrome in early-onset RP with hearing abnormalities. It is also crucial to refer all suspected USH cases to otolaryngologists for early rehabilitation with cochlear implants and thereby better development of cognitive skills. On the contrary, all patients diagnosed with USH or deaf-mute at otolaryngologists or child developmental clinics should also be referred for ophthalmic assessment, rehabilitation, and training. Early visual and hearing rehabilitation are crucial.

Author contributions

The corresponding author states that authorship credit of this manuscript was based on 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. All listed authors met conditions 1, 2, and 3. All persons designated as authors qualify for authorship, and all those who qualify are listed. Each author has participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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Conflicts of interest

There are no conflicts of interest.

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