The Egyptian Journal of Otolaryngology

REVIEW Open Access

Audiological findings in usher syndrome according to types

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Abstract

Purpose Usher syndrome (USH) is the most common condition in which hereditary hearing loss and progressive visual impairment occur together. USH is a clinically and genetically heterogeneous syndrome, divided categories according to the degree of hearing loss and the presence or absence of vestibular dysfunction, the age of onset of retinis pigmentosa: type 1 (USH1), type 2 (USH2), and type 3 (USH3) and atypical type. In this study, auditory influence according to the types of Usher syndrome will be examined.

Materials and methods This systematic review was prepared in accordance with the PRISMA 2020 guidelines. Inclusion criteria include studies from 2010 to 2024, articles written in English, and only studies in individuals with Usher syndrome. Exclusion criteria are animal studies, articles not written in English, thesis studies, books, only gene studies and therapy methods. The remaining 31 articles were included in the study.

Results In the included studies, hearing loss was diagnosed according to the ABR and audiometric evaluation results. Congenital moderate to profound hearing loss was observed in USH1 and USH2, while moderate-profound sensorineural hearing loss was observed in USH3 and USH4/Atypical USH. Delays in gross motor skills were reported in USH1 patients during infancy and childhood.

Conclusion It was observed that people with USH have different degrees of sensorineural hearing loss depending on the type of syndrome. The type of amplification used is often a cochlear implant in USH1 patients and primarily a hearing aid in other types. It should be kept in mind that hearing aid users may also be candidates for CI due to the prognosis of the disease and regular audiologic follow-up should be performed in these patients. Based on the literature review, it is thought that genetic evaluation is necessary in newborns and children, regardless of the degree of hearing loss, especially if there is a family history of hearing and vision impairment.

Keywords Usher syndrome, Hearing loss, Sensorineural, Ush1, Ush2, Ush3

Introduction

Usher syndrome (USH) is a recessive disease characterized by congenital bilateral sensorineural hearing loss (SNHL), retinitis pigmentosa (RP) and vestibular areflexia [1]. USH is the most common cause of hereditary hearing-visual disorders and the most common cause of syndromic hearing loss after Pendred syndrome [2, 3]. It also accounts for 3–6% of cases with congenital hearing loss [4–6] and 18% of RP patients [5, 6]. Although the worldwide prevalence is estimated to be 1.6–4.4/10,000, it is thought that the actual prevalence of USH may be higher due to lack of early diagnosis and misdiagnosis [2, 7].

USH is a clinically and genetically heterogeneous syndrome, and sixteen associated loci and thirteen genes have been identified [8]. USH is divided into type 1 (USH1), Type 2 (USH2), type 3 (USH3), atypical type/type 4 subtypes according to the degree and age of onset of hearing loss, age of onset of RP and presence of vestibular dysfunction [9]. USH1 accounts for 33–44% of all USH cases worldwide. MYO7A, USH1C, CDH23,

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PCDH15, USH1G and CIB2 genes were found to be associated with USH1 [10]. USH1 is characterized by congenital severe/profound sensorineural hearing loss occurring within the first decade of life, vestibular dysfunction in the prepubertal period, and RP. This is the subtype with the worst prognosis. Individuals with this syndrome are often candidates for a cochlear implant (CI) [11]. In addition, children with the syndrome are observed to have delays in sitting and walking functions due to vestibular areflexia [9]. USH2 is the most common form of USH, accounting for 56–67% of all USH cases. This subtype is known to be associated with the USH2A, ADGRV1, and WHRN genes [12, 13]. USH2 has a better prognosis than USH1. It is characterized by congenital moderate to severe, usually progressive sensorineural type hearing loss, preserved vestibular function and progressive RP occurring in the pubertal period [11, 14]. People with this subtype often have preserved hearing at low frequencies. They are good candidates for hearing aids [15]. USH3 is the subtype with the lowest prevalence. It is associated with CLRN1, USH3A genes [8, 16]. USH3 is characterized by progressive postlingual hearing loss, postpubertal RP, and variable vestibular function [16, 17]. People with USH3 are candidates for hearing aids and, rarely, CI [18]. Khateb et al. (2018) first described a homozygous variant in the arylsulfatase G gene (ARSG) responsible for atypical USH characterized by progressive SNHL, late-onset RP, and normal vestibular function. They named this variant USH4/Atypical USH [19].

Different auditory findings are observed in different types of Usher syndrome. Therefore, early diagnosis of the disease, genetic evaluation, patient education, selection of the appropriate amplification method and monitoring the progression of the disease with regular follow-up are necessary for the proper management of USH patients. The aim of this review is to compare the auditory findings observed according to different types of Usher syndrome in the literature and to reveal effective treatment and follow-up management.

Materials and methods

This systematic review was prepared in accordance with the 2020 edition of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20].

Literature search

The literature search was carried out in Google Scholar, Pubmed and Science Direct databases between 2010 and 2024 in tittle/abstract format with the keywords "usher syndrome", "hearing loss", "sensorineural", "ush1", "ush2", and "ush3". Three reviewers independently collected the data and confirmed the results.

Eligibility criteria

All studies were assessed for eligibility based on the following Population, Invertion, Comparison and Outcomes (PICO):

(P) Participants consists of patients with different types of USH.
(I) Intervention includes audiological findings.
(C) Comparison was made according to USH1, USH2, USH3 and USH 4/atypical USH.
(O) Treatment and follow-up methods for different USH types were presented.

Inclusion criteria include articles written in English, and only studies in individuals with Usher syndrome. Exclusion criteria are animal studies, articles not written in English, thesis studies, books, only gene studies and therapy methods. In addition, there is no restriction on age groups in this study.

Data analysis

Due to the heterogeneity in the presentation of data, a statistical meta-analysis of these results was not possible. The results were presented descriptively.

Result

In the literature search, 1253 search results were obtained. Articles were excluded: 142 reviews, systematic reviews and meta-analyses, 42 books, 67 animal studies, 17 not written in English, 1 non-openaccess study. Of the remaining 984 articles, 599 were duplicates. Of the remaining 385 articles, 342 were excluded after reading the abstract because they were not suitable for the article. Forty-three articles that met the inclusion criteria were reviewed and 12 of them were excluded because they were not suitable for the study. Reasons for exclusion: ıt only examines retinis pigmentosa, it consists of a patient population with additional malformations and additional syndromes other than USH, it does not include audiologic findings of the patients and only includes the quality of life of the patients. The remaining 31 articles were included in the study. Integrated review flow is given in Fig. 1.

According to the results of the integrated review, auditory influence differs according to the types of Usher syndrome. Information about the included articles is given in Table 1.

According to the PRISMA checklist, the quality score of the study was obtained at a moderate level (20 points).

Usher syndrome type 1

Filson et al. [23] examined a newborn who underwent ABR testing due to family suspicion in their case study.

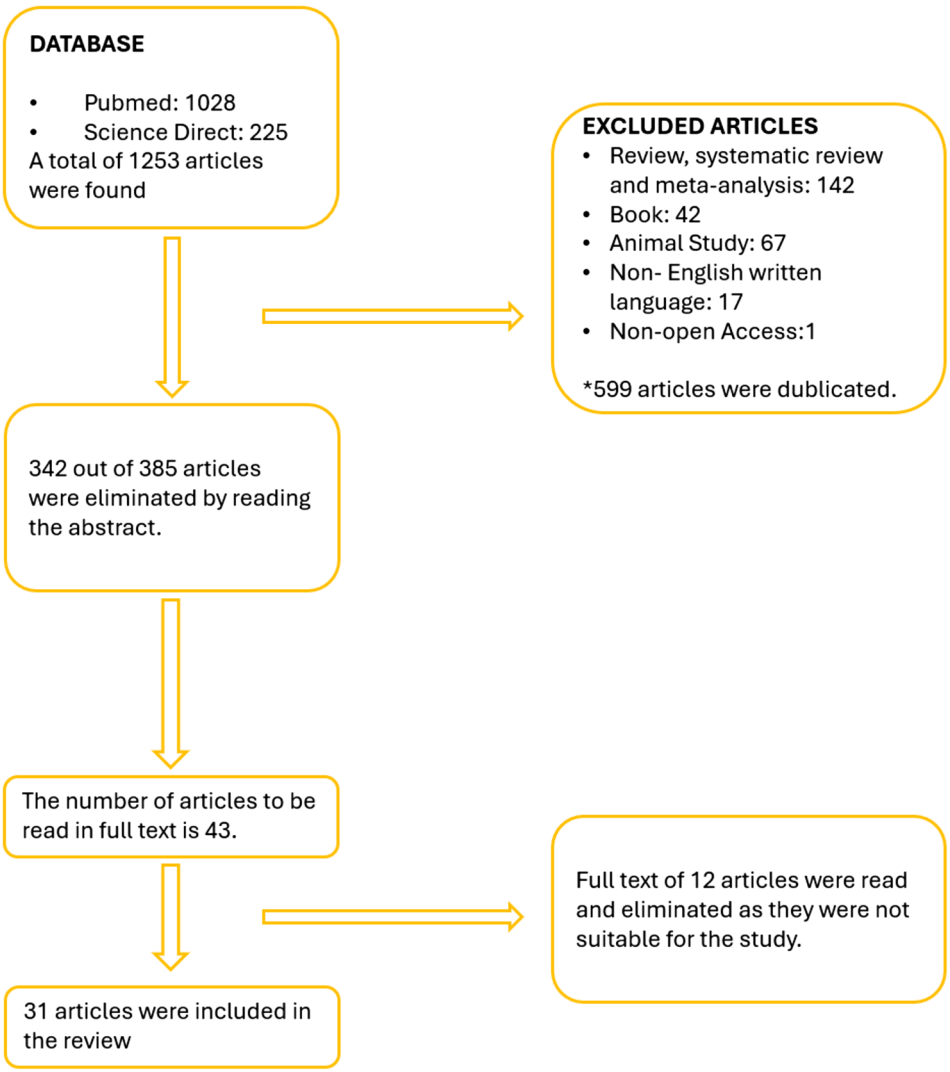

Fig. 1 Article selecting flow diagram

In the evaluation, bilateral very profound SNHL was observed in the patient. It was thought that the motor function delays in the patient's history could be related to vestibular system involvement and genetic evaluation was recommended to the patient. As a result of the genetic evaluation, the unconventional Myosin VII-A (MYO7A) gene associated with USH1 was detected [23]. Similarly, in the study by Ramzan et al. [9], genetic examination was performed on two cousins, one of whom had congenital severe hearing loss and the other had congenital moderate-severe hearing loss according to ABR test results and weakness in motor functions. As a result of the examination, the MYO7A gene was detected [9]. Yoshimura et al. [37] evaluated the presence of USH1 disease in cases with profound hearing loss who did not yet have visual symptoms with mutation analysis of the MYO7A gene. Eighty Japanese children with congenital/early onset severe/profound hearing loss were included in the study. No vestibular complaints were observed in any of the subjects. One child was diagnosed with USH1 with MYO7A mutation analysis. This study emphasized that MYO7A mutation analysis could be a tool for early diagnosis of USH1 [37].

In the study by Imtiaz et al. [1], 3 out of 6 siblings in a family with consanguineous marriage were included due to hearing loss and presence of RP. ABR and visual reinforcement audiometry were performed on all 3 patients before cochlear implant surgery. Within the scope of

Table 1 Summary of articles included in the study

Article name and authors	Syndrome type	Objective	Participants	Evaluation	Results
Identification and computational analysis of USH1C and SLC26A4 variants in Pakistani families with prelingual hearing loss Noman M. ve ark. (2020) [21]	Type 1	Consanguineous marriage effect	–	Audiologic evaluation Tandem walking and Romberg test Ophthalmologic evaluation	GCNF-01-USH1 observed relationship
Compound heterozygous MYO7A mutations segregating Usher syndrome type 2 in a Han family Zong L. ve ark. (2016) [22]	Type 2	To find the mutated gene in a family with autosomal recessive hearing loss and RP findings	7 family members (4 affected and 3 unaffected) were included	Audiologic evaluation Ophthalmologic evaluation Genetic evaluation	3 individuals with congenital profound hearing loss. USH2 was diagnosed in genetic evaluation
Clinical Presentation of Usher Syndrome Type 1B (USH1B) in a 10-Month-Old: A Case Report Filson M.J. ve ark. (2023) [23]	Type 1	To make a case presentation of a person diagnosed with USH	10-month-old baby	Tympanometric evaluation ABR Vestibular evaluation Ophthalmologic evaluation Genetic evaluation	The patient has normal middle ear function Bilateral ABR responses are consistent with severe SNHL CI was recommended for the patient
Clinical Presentation of Usher Syndrome Type 1B (USH1B) in a 10-Month-Old: A Case Report Markova T.G. ve ark. (2022) [24]	Type 2	To analyze audiogram data in people with hearing loss with mutations in the USH2A gene	Thirteen people (11 children, 2 adults) with mutations in the USH2A gene and bilateral moderate-to-profound hearing loss	Immitansmetric evaluation OAE ABR ve ASSR (under 3 years old) Pure tone audiometry Ophthalmologic evaluation	ABR thresholds averaged 55–60 dB nHL and interpeak latencies were within normal limits ASSR thresholds were compatible with ABR The PTA is between 51.25–66.25 dB. Hearing loss with a slight decrease in high frequencies
Utility of whole exome sequencing in the diagnosis of Usher syndrome: Report of novel compound heterozygous MYO7A mutations Ramzan K. ve ark. (2018) [9]	Type *1*	Gene screening and diagnosis of a person with congenital hearing loss	The affected person and his brother	Tympanometric evaluation DPOAE ABR Behavioral audiometry Ophthalmologic evaluation Genetic evaluation	No response to ABR and behavioral audiometry Diagnosis of severe SNHL
A combination of two truncating mutations in USH2A causes more severe and progressive hearing impairment in Usher syndrome type IIa Hartel B.P. ve ark. (2016) [25]	Type 2	Presenting the audiometric phenotype of 110 USH2 patients (10 years)	110 people diagnosed with USH2 (mean age 44 years)	Audiovestibular evaluation Ophthalmologic evaluation	Progressive hearing loss Hearing loss increases towards higher frequencies
A Novel Frameshift Mutation of the USH2A Gene in a Korean Patient with Usher Syndrome Type II Boo S.H. ve ark. (2013) [26]	Type 2	To identify a novel mutation in USH2A detected in a female patient	34-year-old woman	Audiometric evaluation ABR Genetic evaluation	Congenital bilateral moderate-to-profound hearing loss Bilateral ABR thresholds are 60 dBHL

Table 1 (continued)

Article name and authors	Syndrome type	Objective	Participants	Evaluation	Results
USH1G with unique retinal findings caused by a novel truncating mutation identified by genome-wide linkage analysis Imtiaz F. ve ark. (2012) [1]	Type 1	It was conducted to diagnose three siblings with RP	3 siblings from RP	Audiometric evaluation ABR Tandem walking and Romberg test Ophthalmologic evaluation Genetic evaluation	Congenital bilateral profound SNHL was found in three siblings CI was performed
Outcomes of Late Implantation in Usher Syndrome Patients Hoshino A.C.H. ve ark. (2017) [4]	Type 1	To investigate whether late implanted patients diagnosed with USH1 benefit from CI	110 children diagnosed with USH1 and on CI	Audiologic evaluation before and after CI	Before CI, mean PTAs were 103 dB and speech perception was achieved in only 4 patients After CI, mean PTAs were 35 dB and speech perception was not achieved in only 2 patients.3 children stopped using CI
Cochlear Implantation in Children with Usher's Syndrome: A South Asian Experience Nair G. ve ark. (2020) [5]	–	To compare rehabilitation outcomes of CI users with and without USH syndrome	A control group of 27 CI users (1–6 years) with USH syndrome and 30 CI users without additional problems	Evaluation with CAP and SIR scores (3, 6, 9, and 12 months) Tests to assess quality of life	According to CAP and SIR scores, the control group was better However, both groups benefited from rehabilitation
Genotype–phenotype correlation in patients with Usher syndrome and pathogenic variants in MYO7A: implications for future clinical trials Galbis-Martinez L. ve ark. (2021) [10]	Type 1, 2 and atypical type	To retrospectively describe the phenotype of mutations detected in 67 USH patients and correlate them with genotype	62 people diagnosed with USH1 and USH2 (with MYO7A mutation)	Audiologic evaluation Ophthalmologic evaluation Genetic evaluation	It was defined as atypical type in one person, type 2 in two people, and type 1 in the remaining people The average age at diagnosis was 14.86 ± 10.37 years, and the diagnosis of hearing loss was 11.83 ± 9.1 months
Frequency of Usher syndrome in two pediatric populations: Implications for genetic screening of deaf and hard of hearing children Kimberling W.J. ve ark. (2010) [27]	Type 1 and 2	To determine prevalence in the pediatric population and demonstrate the feasibility of adding gene screening to the newborn hearing screening procedure	133 children using CIs in a school for the hearing impaired	Genetic evaluation	15 children were diagnosed with USH. It was concluded that adding gene screening to the newborn hearing screening procedure would be beneficial
Identification of a novel homozygous ARSG mutation as the second cause of Usher syndrome type 4 Abad-Morales V. ve ark. (2020) [28]	Type 4	It describes a new mutation	44 year old woman	Audiological evaluation Ophthalmological evaluation Genetic evaluation	Bilateral moderate to severe SNHL was found. SAT was 45 dB in the right ear and 40 dB in the left ear, while SRT was 50 dB in the right ear and 40 dB in the left ear
Genetic analysis of Tunisian families with Usher syndrome type 1: toward improving early molecular diagnosis Ben-Rebeh I. ve ark. (2016) [7]	Type 1	Genetic analysis of USH cases in 4 consanguineous families	28 people from four related families and people diagnosed with USH1 as the control group	Audiological evaluation Caloric test Ophthalmological evaluation Genetic evaluation	Bilateral very severe SNHL was observed in 12 people. As a result of the genetic evaluation, USH1 was diagnosed

Table 1 (continued)

Article name and authors	Syndrome type	Objective	Participants	Evaluation	Results
USH2 Caused by GPR98 Mutation Diagnosed by Massively Parallel Sequencing in Advance of the Occurrence of Visual Symptoms Moteki H. ve ark. (2015) [29]	Type 2	Genetic screening was performed on 194 people with hearing loss It was intended to provide information about two people (siblings) with the GPR98 mutation	194 individuals with hearing loss	Audiological evaluation Caloric test and cVEMP Ophthalmological evaluation Genetic evaluation	Both siblings had moderate hearing loss decreasing towards high frequencies. Both siblings were diagnosed with USH2 as a result of genetic evaluation
Severe or Profound Sensorineural Hearing Loss Caused by Novel USH2A Variants in Korea: Potential Genotype–Phenotype Correlation Lee S.Y. ve ark. (2020) [11]	Type 2	To investigate two novel USH2A mutations associated with severe-to-profound SNHL in two different families	2 individuals (46-year-old male and 34-year-old female) with postlingual hearing loss and suspected USH2	Audiological evaluation Temporal BT Ophthalmological evaluation Genetic evaluation	Bilateral severe SNHL was observed in the male patient. In the female patient, severe SNHL was observed in the left ear and profound SNHL was observed in the right ear. Both individuals were diagnosed with USH2
Outcomes of cochlear implantation in children with Usher syndrome: a long-term observation Remjasz-Jurek A. ve ark. (2023) [6]	Type 1 and 2	To observe the postimplantation outcomes of children with USH for 10 years	35 children with USH (31 with USH1 and 4 with USH2) and 46 non-syndromic children	Audiological evaluation OAE ABR ASSR Vestibular evaluation Ophthalmological evaluation Temporal BT	Congenital profound hearing loss was observed in patients with Type 1, and severe hearing loss was observed in patients with Type 2. ASSR thresholds above 100 dB were obtained
A novel DFNB31 mutation associated with Usher type 2 syndrome showing variable degrees of auditory loss in a consanguineous Portuguese family Audo I. Ve ark. (2011) [30]	Type 2	Performing genetic screening in people with autosomal recessive RP	4 siblings	Audiological evaluation Ophthalmological evaluation Genetic evaluation	Bilateral moderate-to-severe hearing loss decreasing towards high frequencies was observed in 1 sibling. Postlingual and severe hearing loss was found in the other siblings
Usher Syndrome: Characteristics and Outcomes of Pediatric Cochlear Implant Recipients Jatana K.R. ve ark. (2013) [31]	–	To examine the speech performance and communication method of children with USH using CI	26 children diagnosed with USH and using CI	Speech Recognition Test	All 12 children who received bilateral implants and 42.9% of those who received unilateral implants primarily used verbal communication
Combined Presence in Heterozygosis of Two Variant Usher Syndrome Genes in Two Siblings Affected by Isolated Profound Age-Related Hearing Loss Borgese N. ve ark. (2023) [32]	–	To investigate the cause of hearing loss in two siblings over the age of 70 with severe SNHL	Two siblings	Audiological evaluation ABR Ophthalmological evaluation Vestibular evaluation MRI	Bilateral profound hearing loss was observed and bilateral CI was applied
Usher syndrome Type I in an adult Nepalese male: a case report Sahu S. ve ark. (2017) [33]	Type 1	Audiological findings in an adult with congenital hearing loss and night bilindense due to RP	30 year old male	Audiological evaluation Ophthalmological evaluation	Bilateral profound SNHL was observed. A diagnosis of USH1 was made

Table 1 (continued)

Article name and authors	Syndrome type	Objective	Participants	Evaluation	Results
Novel and Recurrent MYO7A Mutations in Usher Syndrome Type 1 and Type 2 Rong W. ve ark. (2014) [14]	Type 1 and 2	To report three novel mutations of MYO7A in three families with USH Types 1 and 2	7 people	Audiological evaluation Vestibular evaluation Ophthalmological evaluation Genetic evaluation	Bilateral moderate-severe SNHL was observed
A homozygous MYO7A mutation associated to Usher syndrome and unilateral auditory neuropathy spectrum disorder Xia H. ve ark. (2017) [34]	Type 1	To identify the gene that causes USH syndrome in the family	5 family members Control group consisting of 200 people	Immittancemetric evaluation Audiological evaluation ABR TEOAE/DPOAE Ophthalmological evaluation Genetic evaluation MRI	Congenital bilateral profound SNHL was observed in both patients, but MRI findings were normal and there were no acoustic reflexes, ABR responses, or TEOAE. While DPOAE was not found in the left ear of both patients, it was observed in the right ear, and this finding is compatible with ANSD. According to the results, USH1 was diagnosed
Hearing Loss with Vision Impairment: Usher Syndrome. A Case of the East Democratic Republic of Congo Edouard A.M. ve ark. (2023) [35]	Type 2	Case report of a patient with hearing loss and visual impairment	35 year old male	Immittancemetric evaluation Audiological evaluation Vestibular evaluation Ophthalmological evaluation Neurological evaluation	Bilateral moderate-to-severe sensorineural type hearing loss decreasing towards high frequencies was observed, and the patient was diagnosed with USH2. Hearing aid and genetic counseling were recommended to the patient
Targeted exome sequencing reveals novel USH2A mutations in Chinese patients with Simplex Usher syndrome Shu H. ve ark. (2015) [36]	Type 2	To conduct gene screening in two USH families and evaluate this method as a diagnostic tool for USH patients	2 people affected by the syndrome and 4 people unaffected	Audiological evaluation Ophthalmological evaluation Genetic evaluation	Bilateral moderate-severe hearing loss was observed in 1 case, while mild hearing loss was observed in 1 case
An Usher syndrome type 1 patient diagnosed before the appearance of visual symptoms by MYO7A mutation analysis Yoshimura H. ve ark. (2013) [37]	Type 1	To conduct gene screening to examine whether USH syndrome is present in children with non-syndromic severe and profound hearing loss before visual impairments occur	80 children with hearing loss and no vestibular and vision-related problems and 190 people with normal hearing were included	Pure tone audiometry ASSR Ophthalmological evaluation Genetic evaluation	Out of 80 children, 2 children were diagnosed with USH
Simultaneous bilateral cochlear implantation in a five-month-old child with Usher syndrome Alsanosi A.A. (2015) [38]	–	To report the development after bilateral CI in an infant diagnosed with USH at 5 months of age	5 month old baby boy	Free field evaluation	A diagnosis of bilateral profound hearing loss was made. Since there was no benefit from the hearing aid, CI was applied

Table 1 (continued)

Article name and authors	Syndrome type	Objective	Participants	Evaluation	Results
Hearing impairment caused by mutations in two different genes responsible for nonsyndromic and syndromic hearing loss within a single family Niepokój K. ve ark. (2018) [39]	Type 2	Conducting genetic screening on a family diagnosed with hearing loss and finding out which gene causes it	3 participants	Audiological evaluation OAE ABR Genetic evaluation	There is progressive hearing loss and hearing aid use. As a result of genetic evaluation, USH2 was diagnosed
Delayed diagnosis of a patient with Usher syndrome I C in a Louisiana Acadian family highlights the necessity of timely genetic testing fort he diagnosis an management of congenital hearing loss Umrigar A. ve ark. (2017) [40]	Type 1	Case report about the difficulties encountered in the diagnosis and management of children presenting with congenital hearing loss	A patient with congenital hearing loss and recent onset of RP	Genetic evaluation	According to the patient's ABR result, profound SNHL was found. The patient's congenital hearing loss and progressive RP suggested USH1, and as a result of the evaluation, Type 1 was diagnosed. Patients underwent bilateral CI
Audiological findings in 100 USH2 patients Abadie C. ve ark. (2012) [41]	Type 2	To analyze audiological data of 100 USH2 patients. To examine the relationship between genotypes and hearing loss	100 patients diagnosed with USH2	Audiological evaluation	SNHL was observed in all patients. There is moderate hearing loss, which mostly decreases towards higher frequencies
A rare case of type 3 usher syndrome with bilateral cystoid macular edema treated with topical dorzolamide Puthalath A. ve ark. (2021) [16]	Type 3	To report a clinically diagnosed case of USH3	30-year old woman	Audiological evaluation Vestibular evaluation Ophthalmological evaluation	Bilateral moderate-severe SNHL was observed in the patient, and vestibular evaluation results were normal. Late-onset RP is available

the study, ABR test was performed with click stimulus. For ophthalmological examinations, dilated funduscopy, electroretinography (ERG), and visual field were evaluated. Vestibular function was assessed using tandem walking ability and the Romberg test. Multipoint linkage analysis of the genetic evaluation of three affected patients, three unaffected siblings and their parents identified a disease focus on chromosome 17q24.3-q25.3. Patient-1 (18 years old) underwent CI surgery at the age of 6. Patient-1, whose cognitive skills were reported to be normal, was reported to have delayed speech development and motor skills in infancy. The patient's first RP symptom was night blindness and difficulty in visual fixation was reported. Patient-2 (9 years old) underwent CI surgery at the age of 2 due to congenital hearing loss. The patient's history included delayed motor skills and frequent falls. No abnormal findings were observed in the patient's previous ophthalmologic examination. Patient-3 (6 years old) underwent CI surgery at the age of 2 due to congenital hearing loss. The patient has a history of falls. Although cognitive development was normal, severe speech delay was reported. In the genetic evaluation, all 3 patients were diagnosed with USH1 and heterozygous carrier status was observed in the parents and 3 unaffected siblings. [1].

In the study by Xia et al. [34], unaided sitting and walking were observed at the age of 3–4 in two siblings with congenital severe hearing loss in a Chinese family, and night blindness was reported in these individuals at later ages. Acoustic reflex (AR), Transient Evoked Otoacoustic Emission (TEOAE), ABR and magnetic resonance imaging (MRI) were performed on individuals with USH1 syndrome. As a result of the evaluation, AR and ABR responses could not be obtained in two individuals with normal MRI findings. In TEOAE evaluation, no response was obtained in the left ear, but TEOAE responses were obtained in the right ear. Subsequently, the results were consistent with the diagnosis of unilateral (right ear), Auditory Neuropathy Spectrum Disorder (ANSD) were obtained in 2 people. Neither sibling used CI or hearing aids. In the genetic evaluation, the MYO7A c.3696_3706del variant in the siblings was confirmed by Sanger sequencing. The variant was not present in 200 healthy controls of the same ethnic origin. Therefore, it was thought that the variant could be effective in USH1 [34]. Based on these results, we think that it would be useful to evaluate USH1 patients in terms of ANSD.

In the study conducted by Noman et al. [21] to solve the genetic cause of hearing loss in two large consanguineous families from Pakistan, although there was no clinical report, hearing loss was reported in all affected individuals during childhood. As a result of the audiometric examination of 6 individuals,it was revealed that individuals affected by the GCNF-01 family had a very severe HL phenotype for all tested frequencies, while individuals affected by the GCNF-03 family had moderate to profound HL [21].

In the study examining 28 USH 1 patients from 4 Tunisian families in all patients, audiometric evaluation revealed bilateral profound hearing loss, vestibular disorder in caloric testing, and motor weaknesses such as late onset of independent sitting and late walking in childhood. Retinal degeneration, which began in childhood, was detected in all patients. In genetic analysis, a total of three different new pathogenic mutations were detected by direct sequencing of MYO7A, USH1C, and PCDH15 [7]. The 30-year-old male case reported by Sahu presented with slowly progressive night blindness. It was stated that the patient's older brother had also been deaf and mute since childhood. In his audiological evaluation, bilateral profound SNHL was observed [33].

In the study examining the performance of 10 USH1 patients before and after cochlear implant use, the mean age of the patients at the time of cochlear implant surgery was 18.9, and their mean PTA was 103 dB. After surgery, mean PTA increased to 35 dB, and speech discrimination scores increased to 40%. Three patients discontinued cochlear implant use [4]. Nair G. et al. [5] compared speech intelligibility and auditory perception skills in 27 CI users with USH and 30 CI users without any additional disability. Category of Auditory Performance (CAP) and Speech Intelligibility Rating (SIR) tests were performed at 3, 6, 9, and 12 months. As a result of the evaluations, patients with CI without any disability were found to have better auditory perception (CAP) and speech intelligibility (SIR) than patients with CI with USH. In addition, improvements were observed in the outcomes of CI patients with ICH who received auditory-verbal therapy in the following period [5].

USH1 patients are candidates for CI because they have congenital severe to profound hearing loss. Studies have shown that USH patients benefit from CI [4, 5, 31, 38]. CI success depends on many factors and these include age at diagnosis of hearing loss, residual hearing, age at implantation, auditory exposure prior to CI, duration of CI use, auditory rehabilitation, and family support.

Usher syndrome type 2

Moteki et al. [29] included 194 individuals with hearing loss from unrelated families and found a mutation in the GPR98 gene in 2 siblings. Audiometric evaluation of the siblings showed moderate hearing loss with a decline higher frequencies and no progression in hearing loss was observed over a 10-year period. Although the siblings' fundus examinations were normal, impaired responses were observed in their electroretinograms [29].

Audo et al. [30] evaluated the genetic disorder in a Portuguese family in which 4 out of 5 siblings had rod-cone dystrophy and hearing loss of varying degrees. The index patient, aged 60, was diagnosed with RP at the age of 20, which caused night vision difficulties, narrowing of the visual field, and a slight decrease in visual acuity. No hearing loss was reported in the initial medical questionnaire, but the patient reported hearing loss and tinnitus in recent years. The audiometric evaluation revealed bilateral moderate hearing loss, and the patient was recommended hearing aids. Similarly, it was stated that hearing loss occurred in the affected siblings at similar periods. The genetic evaluation diagnosed the individuals with Usher type 2, which is associated with a mutation in DFNB31 [30]. Lee et al. [11] examined the USH2A variant and clinical phenotypes in 2 Korean families with severe and profound sensorineural hearing loss. Evaluation of USH2 patients with postlingual hearing loss and RP revealed the indication for the use of cochlear implants in these individuals. Typical RP findings were observed in the ophthalmic examination. The study showed that variants of the USH2A gene may cause a more severe audiological phenotype [11]. Hartel et al. [25] evaluated the audiological evaluation results of 110 Usher syndrome type IIa patients with different genotypes in their study. As a result of the study, it was found that the hearing loss of patients with Usher syndrome type IIa was congenital, decreasing in high frequencies (~ 15 dB in low frequencies/~ 60 dB in high frequencies), and progressive (~ 0.4 dB/year in low frequencies and ~ 7 dB/year in high frequencies). In addition, Patients with two truncating mutations in USH2A show more severe and progressive sensorineural HI compared to Usher type IIa patients without two truncating mutations [25]. Zong et al. [22] presented the audiological, ophthalmological and genetic evaluation results of a family that came to genetic counseling due to congenital hearing loss. Seven family members, 3 affected and 4 unaffected, were included in the evaluation. Total hearing loss affecting all frequencies was observed in all affected family members and temporal CT results were obtained normal. RP symptoms occur in the late period, but are present in cases with progression of RP. The gross motor development of the affected individuals was obtained normally and there were no balance problems. As a result of the genetic evaluation, the individuals were diagnosed with USH2 associated with the new mutation in the c.3924 + 1G > C compound found together with c.6028G > A in the MYO7A gene [22].

Boo et al. [26] described a 34-year-old Korean woman with a mutation in the USH2A gene, with the typical clinical presentation of USH2.The patient applied to the clinic due to bilateral hearing loss since childhood. The patient does not use hearing aids. In addition to the hearing loss complaint, the patient had night blindness since adolescence and visual field loss since the age of 17. The visual impairment was progressive and the patient was blind when he was admitted to the hospital. The patient did not complain of dizziness. The patient underwent pure-tone audiometric evaluation and ABR were recorded. According to pure-tone averages, the patient was observed to have bilateral, moderate, SNHL decreasing towards high frequencies. The ABR thresholds were found to be 60 dB HL bilaterally. Bithermal caloric test, CT and MRI showed normal findings [26]. Umrigar et al. [40] presented a case study of a 17-year-old patient with profound hearing loss who was diagnosed with RP at the age of 16. The patient's newborn hearing screening and subsequent ABR test were found to be consistent with bilateral profound hearing loss. The patient was informed about the cochlear implant and was given American Sign Language training. The patient had relatives with profound hearing loss and late-onset visual impairment. In the genetic evaluation, 12 individuals were deaf only and 4 had blindness at different ages of onset (15–30 years). In the genetic evaluation, the proband was found to be homozygous for the USH1C c.216G > A point mutation that causes Usher syndrome type 1C. The patient underwent bilateral cochlear implant surgery, and hearing was within normal limits in the free-field evaluation with the cochlear implant after surgery [40]. Niepokój et al. [39] presented the case of an index patient, his sibling and his cousin who had mutations in genes associated with syndromic and non-syndromic hearing loss. Immitansmetric assessment, OAE and ABR tests were performed on the siblings in the early stages of their lives, and hearing levels were obtained above 60 dB in both children. In the audiological assessment performed 2 years later, it was observed that the hearing thresholds increased to 90–95 dB in the older child and remained constant in the younger child. It was stated that both siblings used hearing aids. In the molecular analysis, it was found that the siblings had USH2 associated with a pathogenic mutation in the USH2A gene. In the cousin, who was suspected of having USH due to family history, a mutation was observed in the GJB2 gene associated with non-syndromic hearing loss. In the study, it was emphasized that the phenotypic differences in genes associated with HL pathogenesis may make diagnosis difficult [39] Alsanosi [38] evaluated the success of a cochlear implant in a 5-month-old baby with Usher syndrome who underwent simultaneous bilateral cochlear implantation in a case study. The baby had a very severe congenital hearing loss. The baby underwent a cochlear implant early in order to support his hearing before vision problems began. The baby benefited from the implant and showed audiologic

development appropriate for his chronological age at 14 months of age [38].

Markova et al. [24] reported bilateral mild to moderate hearing loss in a group of 13 SNHL patients caused by the USH2A gene. It was stated that 7 of these patients were non-syndromic in the first decade of their lives [24].

Usher syndrome type 3 and Usher syndrome type 4/ atypical type

Puthalath et al. [16] studied a 30-year-old patient who complained of bilateral vision loss for the last 1 month. The patient was diagnosed with USH3 due to hearing loss that increased in the last 10 years and RP findings that started 5 years ago and showed progression. Ophthalmic examination at the age of 15 and hearing at birth and early childhood were reported as normal. There was no risk in the family history. Fundus examination revealed arteriolar attenuation and macular edema findings consistent with RP. Audiological evaluation revealed bilateral moderate to severe sensorineural hearing loss. Vestibular evaluation was normal. The patient was diagnosed with USH3. Long-term audiologic follow-up is also important in type 3 because of the progression of hearing loss [16].

Abad-Morales V. et al. [28] evaluated a 44-year-old case who presented to the clinic with progressive visual impairment and a history of hearing loss since infancy. Fundus examination revealed increased bone spicule-like pigmentation supporting retinal pigment disorder. Audiometric examination revealed moderate-to-severe bilateral sensorineural hearing loss, while vestibular function was reported as normal. All results remained similar 3 years later. The case, whose parents were consanguineous, had no other family history of similar disorders. Genetic evaluation considered the most likely case to be the c.130G > A variant in ARSG reported by Khateb [28].

Discussion

Usher syndrome type 1

When the general symptoms of USH1 patients are examined, severe to profound hearing loss, late-onset RP, delay in motor skills such as sitting and walking in early childhood, history of frequent falls, and vestibular arreflexia are seen [1, 7, 42].

In the literature, studies examining USH1 patients with ABR in Ramzan's study, moderate to severe hearing loss was observed in the patient, while in all other studies, profound sensorineural hearing loss was observed [1, 9, 23, 34, 37]. This suggests that, contrary to the literature, early hearing loss in USH1 patients may be less severe than expected.

[4, 5, 21, 33] examined the hearing of USH1 patients through audiometric evaluation in their studies. As a result of the studies, Noman et al. [21] obtained moderate-to-severe sensorineural type hearing loss, while other studies obtained severe-to-profound hearing loss, in accordance with the literature.

In case studies evaluating patient success after CI surgery, [4] reported improvement in postoperative speech and pure tone audiometry results of USH1 patients. However, it was thought that it would be more useful to compare this situation with CI users without USH1. Because according to our clinical follow-ups, we observe that non-syndromic CI patients have higher average speech discrimination scores (40%) than those reported in this study. In the study by [5], it was revealed that CI patients without USH1 were more successful than CI patients with USH1 in the early period, but the results were similar in the long term due to the effect of the rehabilitation process. In addition, it is known that cognitive functions are occasionally affected in this patient group and it should be taken into account that cognitive skills can affect auditory perception processes. More detailed evaluation of cognitive skills in USH patients by experts and examination of their effects on auditory skills will contribute to the literature.

Usher syndrome type 2

In the literature, studies examining USH2 patients with audiometric evaluation, [25, 29, 30] reported that patients had moderate sensorineural hearing loss, while [11, 22] revealed severe to profound hearing loss.

In studies evaluating USH2 patients with ABR, [40] found profound hearing loss, while [26, 39] reported moderate hearing loss.

In one of the cases reported by [39], hearing loss progressed from moderate to severe after 2 years. Considering other studies reporting severe to profound hearing loss, annual follow-up was considered necessary in order not to be late for CI surgery.

Usher syndrome type 3 and Usher syndrome type 4/ atypical type

The audiological and vestibular findings of the USH3 and USH4 patients listed above were observed to be similar. At this point, the distinguishing factor is genetic evaluation. It should be kept in mind that in these types of cases, an increase in hearing loss is observed in the long term and that they may be suitable candidates for CI.

Conclusion

In the integrated review, it was observed that people with USH have different degrees of sensorineural hearing loss depending on the type of syndrome. The type of amplification used is often a cochlear implant in USH1 patients and primarily a hearing aid in other types. It should be kept in mind that hearing aid users may also

be candidates for CI due to the prognosis of the disease and regular audiologic follow-up should be performed in these patients. Based on the integrated review, it is thought that genetic evaluation is necessary in newborns and children, regardless of the degree of hearing loss, especially if there is a family history of hearing and vision impairment. For the long-term success of the rehabilitation process of individuals with Usher syndrome, it is recommended to use the necessary rehabilitative methods together with hearing aids and CI before the loss of two basic senses (hearing and vision).

Limitations

Because there are so few research on individuals with isolated USH in the literature, the number of included papers is lower than anticipated.

Authors' contributions

M.B.B: designing, searching, writing, editing. R.Y: searching, writing. N.T.E: searching, writing, editing.

Funding

None.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 12 March 2025 Accepted: 19 December 2025
Published online: 03 January 2026

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