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Long-Term Outcomes of Cochlear Implantation in Usher Syndrome

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Objectives: Usher syndrome (USH), characterized by bilateral sensorineural hearing loss (SNHL) and retinitis pigmentosa (RP), prompts increased reliance on hearing due to progressive visual deterioration. It can be categorized into three subtypes: USH type 1 (USH1), characterized by severe to profound congenital SNHL, childhood-onset RP, and vestibular areflexia; USH type 2 (USH2), presenting with moderate to severe progressive SNHL and RP onset in the second decade, with or without vestibular dysfunction; and USH type 3 (USH3), featuring variable progressive SNHL beginning in childhood, variable RP onset, and diverse vestibular function. Previous studies evaluating cochlear implant (CI) outcomes in individuals with USH used varying or short follow-up durations, while others did not evaluate outcomes for each subtype separately. This study evaluates long-term CI performance in subjects with USH, at both short-term and long-term, considering each subtype separately.

Design: This retrospective, observational cohort study identified 36 CI recipients (53 ears) who were categorized into four different groups: early-implanted USH1 (first CI at ≤7 years of age), late-implanted USH1 (first CI at ≥8 years of age), USH2 and USH3. Phoneme scores at 65 dB SPL with CI were evaluated at 1 year, ≥2 years (mid-term), and ≥5 years postimplantation (long-term). Each subtype was analyzed separately due to the significant variability in phenotype observed among the three subtypes.

Results: Early-implanted USH1-subjects (N = 23 ears) achieved excellent long-term phoneme scores (100% [interquartile ranges {IQR} = 95 to 100]), with younger age at implantation significantly correlating with better CI outcomes. Simultaneously implanted subjects had significantly better outcomes than sequentially implanted subjects ($p = 0.028$). Late-implanted USH1 subjects (N = 3 ears) used CI solely for sound detection and showed a mean phoneme discrimination score of 12% (IQR = 0 to 12), while still expressing satisfaction with ambient sound detection. In the USH2 group (N = 23 ears), a long-term mean phoneme score of 85% (IQR = 81 to 95) was found. Better outcomes were associated with younger age at implantation and higher preimplantation speech perception scores. USH3-subjects (N = 7 ears) achieved a mean postimplantation phoneme score of 71% (IQR = 45 to 91).

Conclusions: This study is currently one of the largest and most comprehensive studies evaluating CI outcomes in individuals with USH, demonstrating that overall, individuals with USH benefit from CI at both short- and long-term follow-up. Due to the considerable variability in phenotype observed among the three subtypes, each subtype was analyzed separately, resulting in smaller sample sizes. For USH1 subjects, optimal CI outcomes are expected with early simultaneous bilateral implantation. Late implantation in USH1 provides signaling function, but achieved speech recognition is insufficient for oral communication. In USH2 and USH3, favorable CI outcomes are expected, especially if individuals exhibit sufficient speech recognition with hearing aids and receive ample auditory stimulation preimplantation. Early implantation is recommended for USH2, given the progressive nature of hearing loss and concomitant severe visual impairment. In comparison with USH2, predicting outcomes in USH3 remains challenging due to the variability found. Counseling for USH2 and USH3 should highlight early implantation benefits and encourage hearing aid use.

Key words: Clinical decision-making, Cochlear implantation outcomes, Disease management, Usher syndrome type 1, Usher syndrome type 2, Usher syndrome type 3, Usher syndrome.

Abbreviations: CI = cochlear implant; CMV = cytomegalovirus; dB = decibel; ENG = electronystagmography; IQR = interquartile ranges; PTA = pure-tone average; RP = retinitis pigmentosa; SGN = spiral ganglion neuron; SNHL = sensorineural hearing loss; SPL = sound pressure level; USH = Usher syndrome; USH1 = Usher syndrome type 1; USH2 = Usher syndrome type 2; USH3 = Usher syndrome type 3; VIFs = variance inflation factors.

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INTRODUCTION

Usher syndrome (USH) is an autosomal recessively inherited disease characterized by bilateral sensorineural hearing loss (SNHL) and retinitis pigmentosa (RP), with or without vestibular dysfunction. Subjects with USH experience progressive visual loss from RP for which there is no current treatment, increasing their dependence on hearing for communication. Often, a cochlear implant (CI) is needed to improve speech recognition.

USH is both clinically and genetically heterogeneous and historically divided into three phenotypically different clinical subtypes according to severity and onset of hearing loss and whether vestibular dysfunction is present or not (Table 1) (Smith et al. 1994). The prevalence of USH differs depending on the clinical subtype, with USH1 and USH2 accounting for the greatest proportion of cases. The prevalence of USH is estimated at 4 to 17/100.000 people (Boughman et al. 1983; Kimberling et al. 2010) and occurs in 3 to 6% of children with congenital deafness (Boughman et al. 1983). USH type I (USH1) comprises about one-third of USH subjects, and is characterized by severe to profound congenital SNHL, childhood-onset of RP, and vestibular areflexia. USH type II (USH2) is the most common type, with moderate to severe progressive congenital SNHL and onset of RP in the second decade of life or later, with or without

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TABLE 1. Summary of Usher syndrome subtypes

Usher Type	Hearing Loss	Retinitis Pigmentosa	Vestibular Function	Genetic Subtype	Causative Genes	Protein
Usher I	Severe to profound congenital HL	Onset in the first decade of life	Vestibular areflexia, delayed motor development	USH1B	*MYO7A*	Myosin VIIa
				USH1C	*USH1C*	Harmonin
				USH1D	*CDH23*	Cadherin 23
				USH1F	*PCDH15*	Protocadherin 15
				USH1G	*USH1G*	Sans
Usher II	Moderate to severe congenital HL	Onset in the second decade of life	Possible vestibular defects	USH2A	*USH2A*	Usherin
				USH2C	*ADGRV1*	ADGRV1
				USH2D	*WHRN*	Whirlin
Usher III	Post-lingual variable progressive HL	Variable onset, typically in the second decade of life	Variable vestibular function	USH3A	*CLRN1*	Clarin1

HL, hearing loss; IHC, inner hair cells; OHC, outer hair cells.

vestibular dysfunction. USH type III (USH3) is rare in most populations, accounting for approximately 2 to 4% of all cases, although it is notably more prevalent in Finland and among Ashkenazi Jewish people (Pakarinen et al. 1995; Ness et al. 2003). It displays variable progressive SNHL with the age of onset, usually in the first decade of life, variable onset of RP, and variable vestibular function (Nisenbaum et al. 2022). Recently, USH type IV (USH4) was defined with late-onset SNHL and RP, and uncertain vestibular involvement (Abad-Morales et al. 2020; Peter et al. 2021). While late-onset SNHL and RP could phenotypically be characterized as a form of USH, genetically there is an ongoing debate because there is no clear link between the ARSG protein and the other known Usher proteins (Delmaghani & El-Amraoui 2022). Because of the late-onset hearing loss and mild progression, all currently reported subjects with USH4 do well with hearing aids and none received a CI (Khateb et al. 2018; Abad-Morales et al. 2020; Fowler et al. 2021; Igelman et al. 2021; Peter et al. 2021; Velde et al. 2022). Therefore, USH4 is outside the scope of this article.

To date, nine causative genes have been identified for USH, including five USH1 genes (*MYO7A*, *USH1C*, *CDH23*, *PCDH15*, and *USH1G*), three USH2 genes (*USH2A*, *ADGRV1*, *WHRN*), and one USH3 gene (*CLRN1*, Table 1) (Delmaghani & El-Amraoui 2022). Variants in the USH1 genes are also associated with nonsyndromic autosomal recessively SNHL, including DFNB2, DFNB12, DFNB18A, and DFNB23 (Table 2). Furthermore, variants in *WHRN* are associated with both USH2D and DFNB23. The Usher genes encode a variety of proteins that are organized into an USH protein network. In the inner ear, this protein network plays an essential role in the development and function of inner ear hair cells (Maerker et al. 2008; Yan & Liu 2010). USH1 and USH2 proteins are mainly expressed in hair cells (Nishio et al. 2015), while CLRN1 is also expressed in spiral ganglion neurons (SGNs) (Yan & Liu 2010; Nishio et al. 2015).

Children with USH1, born with a profound hearing loss, are considered ideal candidates for cochlear implantation, as they are diagnosed early, have normal inner ear anatomy, normal cognitive abilities, and the potential for regular speech-language development postimplantation. Early bilateral cochlear implantation leads to the most favorable audiological performance and quality of life in USH1 subjects (Damen et al. 2006; Pennings et al. 2006; Jatana et al. 2013). In subjects with USH2, the progression of hearing impairment leads to insufficient speech recognition and, therefore, inadequate communication with hearing aids over time. For these subjects, (bilateral) CI might be the next step in rehabilitation, enhancing speech recognition and overall quality of life (Hartel et al. 2017). Similarly, subjects with USH3 experience positive outcomes after CI, although hearing outcomes are variable (Pietola et al. 2012).

However, previous studies evaluating CI outcomes in individuals with USH used varying follow-up durations (Damen et al. 2006; Pennings et al. 2006; Hartel et al. 2017). Some studies had a follow-up of only 1 year (Pietola et al. 2012), while others did not evaluate outcomes for each subtype separately (Loundon et al. 2003; Jatana et al. 2013; Alzhrani et al. 2018; Remjasz-Jurek et al. 2023). In addition, as progressive vision loss in individuals with USH amplifies their dependence on auditory perception for communication, assessing the long-term CI performance in this population is crucial. Therefore, this study evaluates CI performance in Dutch individuals with USH, considering each subtype separately at both short-term and long-term.

MATERIALS AND METHODS

Study Design and Population

This retrospective, observational cohort study evaluated CI performance in CI recipients with USH. For this, we assembled a study cohort with genotyped CI recipients. Subjects were included in this cohort when they (1) had a confirmed genetic diagnosis based on monoallelic or biallelic (likely) pathogenic variants in respectively dominant or recessive inherited genes associated with SNHL; (2) received a CI between 2002 and 2021; (3) had at least 1-year of follow-up measurements of the speech recognition. Subjects were excluded from this study if aged ≥70 years at implantation, had a history of other diseases that confound CI performance, or had SNHL related to prenatal TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus) infections, aminoglycoside exposure, otoacoustic trauma, meningitis, or hyperbilirubinemia. One selected USH3 subject had bilateral hypoplasia of the cochlear nerve. Given the previous association between neural degeneration and the USH3 phenotype (Shinkawa & Nadol 1986), we did not exclude this subject from the study.

Subjects for this study were selected from this database based on a clinical diagnosis of USH, including SNHL and RP, confirmed by a genetic diagnosis involving the presence of biallelic (likely) pathogenic variants in one of the known Usher genes. Individuals with SNHL associated with one of the USH1 genes, for which the diagnosis of USH1 or nonsyndromic SNHL was not yet clear, were also included. These individuals

TABLE 2. Study population demographics

Subtype	Gene	Diagnosis	OMIM No.	Subjects N (%)	Ears N (%)	Subgroup	Subjects Per Subgroup N (%)	Ears per Subgroup N (%)	Age at Implantation Median (IQR)	Preoperative Vestibular Function Per Ear N (%)†		Hearing Aid in Ear to be Implanted N (%)
USH1	*MYO7A*	DFNB2	600,060	0	0	USH1 implanted <8 yrs of age*	11 (31.4)	20 (37.7)	13 (11–19) m	Normal	4 (20.0)	17 (85.0)
		USH1B	276,900	10 (28.6)	16 (30.2)					Areflexia	14 (70.0)	
	USH1C	DFNB18A	602,092	0	0					Unknown	2 (10.0)	
		USH1C	276,904	1 (2.9)	1 (1.9)	USH1 implanted ≥8 yrs of age	3 (8.6)	3 (5.7)	29 (24–29) y	Hyporeflexia	1 (33.3)	3 (100.0)
	CDH23	DFNB12	601,386	2 (5.7)	4 (7.2)					Areflexia	2 (66.7)	
		USH1D	601,067									
	PCDH15	DFNB23	609,533	1 (2.9)	2 (3.8)							
		USH1F	602,083									
	USH1G	USH1G	606,943	0	0							
USH2	USH2A	USH2A	276,901	15 (42.9)	20 (37.7)	USH2	17 (48.6)	23 (43.4)	53 (42–63) y	Normal	11 (47.8)	22 (95.7)
	ADGRV1	USH2C	605,472	2 (5.7)	3 (5.7)					Hyperreflexia	5 (21.7)	
	WHRN	DFNB31	607,084	0	0					Hyporeflexia	5 (21.7)	
		USH2D	611,383	0	0					Areflexia	2 (8.7)	
USH3	*CLRN1*	USH3A	276,902	4 (11.4)	7 (13.2)	USH3	4 (11.4)	7 (13.2)	39 (3.0–60) y	Normal	5 (71.4)	6 (85.7)
										Hyporeflexia	1 (14.3)	
										Unknown	1 (14.3)	
	Total			35 (100)	53 (100)		35 (100)	53 (100)	8.0 (1.0–52) y	—	—	48 (90.6)

ENG, electronystagmography; HL, hearing loss; IQR, interquartile ranges; m, months; N, number; NS-SNHL, nonsyndromic sensorineural hearing loss; y, years.

**This group includes also subjects who could not yet be diagnosed with either USH1 or NS-SNHL (N = 10 ears).*

†Tested with ENG which was performed with vestibular caloric, and/or rotary chair testing.

included children <10 years old, and so far, had no symptoms of RP, which still may emerge later in life. Some of the subjects enrolled in this study have been described in previous publications (Plantinga et al. 2005; Damen et al. 2006; Pennings et al. 2006; Hartel et al. 2017).

Given the considerable variability in phenotype observed among the three USH subtypes, we categorized the study population accordingly to analyze each subtype separately. Within the USH1 group, a further distinction was made between early implanted subjects, defined as those who received their first CI ≤7 years of age, and late-implanted subjects, who received their first CI ≥8 years of age. The decision to use the age cutoff of 7 years was informed by previous research indicating that central and peripheral nervous system changes resulting from auditory deprivation can be restored to near-normal levels up to the age of 3.5 to 4.0 years, with some children benefiting from this brain plasticity until the age of 7 years (Sharma et al. 2002; Kral & Sharma 2012).

Data Collection

Demographic factors were collected by chart review and included gender, self-reported age of onset of SNHL, use of hearing aids, learning difficulties, and age at the time of implantation. All preoperative and postoperative audiovestibular examinations were evaluated. Vestibular testing was performed by caloric and rotatory chair testing, using electronystagmography, and the video head impulse test to assess the semi-circular vestibular organs. In some cases, vestibular evoked myogenic potential testing was also performed to evaluate otolith function. A vestibular specialist interpreted the results of these tests, primarily relying on electronystagmography and video head impulse test outcomes, to ascertain the presence of areflexia, hyporeflexia, or normal vestibular function. Results of imaging were included to assess cochleovestibular anomalies. The surgical technique and side of implantation were scored to evaluate surgical factors. The type of implant and electrode were also recorded. The genetic diagnosis was gathered by scoring the variant(s) with the associated protein change(s), type of variant (truncating or missense), and classification according to the American College of Medical Genetics and Genomics (ACMG) association guidelines (Richards et al. 2015). No additional genetic analysis or audiological tests were performed.

Hearing was evaluated by standard pure tone and speech audiometry according to current standards. Speech perception was assessed in quiet with standard monosyllabic (consonant-vowel-consonant) Dutch word lists (Bosman & Smoorenburg 1995) presented at 65 dB SPL. Scores were based on correct repetition of phonemes and were evaluated both aided and unaided. In early implanted children with prelingual SNHL (USH1), behavioral observation audiometry was used to determine pure tone thresholds preimplantation and during the 1-year follow-up. Due to their young ages, speech audiometry could not be performed preimplantation or at the 1-year follow-up in this subgroup.

The pure-tone average (PTA) was calculated using thresholds at 500, 1000, 2000, and 4000 Hz ($PTA_{0.5\text{-}4kHz}$). Not all subjects used hearing aids before implantation. We calculated the best-aided PTA and phoneme scores measured at 65 dB SPL to compare the preimplantation hearing performance with the postimplantation CI performance. The best-aided scores combined the aided scores from subjects using hearing aids before implantation with the unaided scores from those not using hearing aids preimplantation. If aided scores were unavailable, unaided scores were utilized instead. From bilaterally implanted subjects, the binaural aided phoneme scores at 65 dB SPL in quiet were collected as well. The postimplantation $PTA_{0.5\text{-}4kHz}$ and phoneme scores at 65 dB SPL were evaluated at three moments in time: after 1 year, ≥2 years (mid-term), and ≥5 years postimplantation (long-term). Excluding the late-implanted USH1 subjects, CI recipients with a phoneme score <70% at least 1-year postimplantation were considered poor performers. Subjects beneath this score were evaluated in more detail.

Data Analysis

Statistical analyses were performed with IBM Statistical Package for the Social Science Statistics 27. A p value <0.05 was considered statistically significant. The Shapiro–Wilk test was used to assess data distribution for normality, and normally distributed data (e.g., PTA-scores, months/years of follow-up) were presented as mean values with SD. The median with interquartile ranges (IQR), was used to present non-normally distributed data (e.g., age at implantation, phoneme scores). The mean PTA and phoneme scores at different follow-up moments were compared with the dependent sample t test. Median phoneme scores at different follow-up time points were compared using the Wilcoxon signed ranged test, while the Mann–Witney U test was used to compare phoneme scores between two distinct subgroups, while the independent sample t test was used to compare age of implantation between two groups. The Kruskal–Wallis test was used to compare median phoneme scores between multiple subgroups. Univariate linear regression analysis was performed to study the correlation of the phoneme scores with the age of implantation. A multiple regression analysis was used to further assess this correlation while correcting for confounders. The variance inflation factors (VIFs) were utilized for multicollinearity testing. All data were analyzed separately for each subtype, with the USH1 group further subdivided into an early-implanted and late-implanted subgroup.

RESULTS

Study Population, Demographics, and Genotype

After evaluation of inclusion and exclusion criteria, 35 subjects were included in this study, of which 25 (71%) were female. Most subjects were diagnosed with either USH1B (29%) or USH2A (43%; Table 2 and Supplementary Table 1 in Supplemental Digital Content, http://links.lww.com/EANDH/B443). For three subjects, distinguishing between USH1D and DFNB12 (in two subjects) or USH1F and DFNB23 (in one subject) proved challenging. This difficulty arises because these children, all under the age of 10, have yet to exhibit visual symptoms, which might still manifest later in life. Despite this ambiguity, these subjects have been categorized as part of the USH1 group.

A total of 38 different variants were identified in seven different USH genes (Table 3). After reevaluation, two variants were classified as a variant of uncertain significance and were present in combination with a pathogenic variant in two subjects (USH1-2, USH2-14). Consequently, these subjects no longer

met the inclusion criteria. However, because both exhibited the characteristic clinical phenotype of respectively USH1 and USH2, involving SNHL along with RP, and in the first case, also areflexia, these individuals were not excluded from the study.

In the study population, a total of 54 cochlear implantations were performed. Among these, 16 subjects received unilateral implantation, while 19 underwent bilateral implantation (8/19 simultaneous and 11/19 sequential). The first CI (USH1-11.1) of subject USH1-11 was excluded from this study due to insufficient clinical data from the initial years following her first implantation, as it was implanted abroad. Consequently, a total of 53 ears were included.

USH Type 1

In the USH1 group, cochlear implantation was performed in 23 ears of 14 subjects. This group was further divided into the following groups: (1) early implanted USH1 subjects, including subjects who received their first CI ≤7 years of age; (2) late-implanted USH1 subjects, who received a first CI at the age of ≥8 years. For the latter group, the goal of implantation was not to achieve sufficient speech recognition, but for the CI to have a signaling function that helps compensate for the deterioration in vision.

Early Implanted Subjects With USH1 • In this subgroup, a total of 20 CIs in 11 subjects were implanted with a median age at implantation of 13 months (IQR = 11 to 19). This subgroup includes subjects diagnosed with RP over the years following CI (N = 8 subjects), and subjects who could not yet be diagnosed with either USH1 or NS-SNHL (N = 3 subjects). In all eight subjects diagnosed with USH1, vestibular areflexia was measured preimplantation in all 14 ears. In the three subjects with biallelic pathogenic variants in CDH23 or *PCDH15* and an uncertain diagnosis, vestibular function was normal in four ears, and in two ears vestibular function was not measured.

In the entire early implanted USH1 group, the preoperative unaided $PTA_{0,5\text{-}4kHz}$ was 102 ± 15 dB HL (N = 15 ears), and the best-aided $PTA_{0,5\text{-}4kHz}$ was 95 ± 16 dB HL (N = 20 ears). At 11 ± 3 months postimplantation, the postoperative $PTA_{0,5\text{-}4kHz}$ significantly decreased to 34 ± 7 dB HL ($p < 0.001$; N = 19 ears). The $PTA_{0,5\text{-}4kHz}$ further decreased to 28 ± 16 dB HL at 4.5 ± 1.3 years ($p = 0.026$; N = 20 ears), and to 22 ± 4 dB HL at 12.0 ± 3.3 years ($p = 0.113$; N = 15 ears; Fig. 1A1). At 4.8 ± 0.9 years after implantation, the median phoneme score at 65 dB SPL in quiet was 94% (IQR = 87 to 100; N = 20 ears), which significantly increased to 100% (IQR = 95 to 100) at 11.8 ± 3.3 years postimplantation ($p = 0.005$, N = 15 ears; Figs. 1A2, A3).

Early implanted USH1 subjects had significantly lower best-aided $PTA_{0,5\text{-}4kHz}$ scores preoperatively compared with subjects with no clear diagnosis (early implanted-USH1/NSHL) with a $PTA_{0,5\text{-}4kHz}$ of respectively 101 ± 15 dB HL and 81 ± 5 dB HL ($p = 0.002$; Fig. 1A1). Long-term follow-up showed no difference in aided $PTA_{0,5\text{-}4kHz}$ postimplantation between the early implanted USH1 subjects and early implanted USH1/NSHL subjects ($p = 0.732$). In addition, no difference was observed between these two groups when comparing phoneme scores at 65 dB SPL in quiet during the middle-term and long-term follow-up ($p = 0.207$ and $p = 0.305$, respectively).

Late-Implanted Subjects With USH1 • This subgroup (N = 3) enrolled subjects who received the first CI at the age of ≥8 years. All three subjects considered cochlear implantation in adulthood upon experiencing profound vision loss due to RP. They had not considered implantation earlier, as two of them were fully engaged in the deaf community. At the same time, the third subject was raised in a developing country and arrived in the Netherlands as an adult. Initially, they all successfully communicated using sign language but experienced increasingly severe (communication) problems as their vision deteriorated, prompting their decision to pursue cochlear implantation.

Within this subgroup, cochlear implantation was, in all cases, single-sided. Vestibular areflexia was measured in two ears, while hyporeflexia was found in one ear. A preoperative unaided $PTA_{0,5\text{-}4kHz}$ and best-aided $PTA_{0,5\text{-}4kHz}$ of respectively ≥120 ± 0 dB HL (N = 3 ears) and 75 ± 9 dB HL (N = 3 ears) was found. The postoperative $PTA_{0,5\text{-}4kHz}$ significantly decreased to 45 ± 13 dB HL ($p = 0.024$, N = 3 ears) at 14 ± 3.5 months postimplantation, after which the PTA was not measured anymore (Fig. 1B1). The preoperative best-aided phoneme score at 65 dB SPL in quiet was measured in two ears with a median score of 0.0% (IQR = 0.0 to 0.0). At 15 ± 3.0 months postimplantation the median phoneme score at 65 dB SPL was 12% (IQR = 0 to 12; N = 3 ears, $p = 0.180$). After this first follow-up, the phoneme scores were not measured again in this subgroup (Figs. 1B2, B3).

At the last follow-up visit, the three late-implanted USH1 subjects were 4.0 to 10.6 years postimplantation, and each of them still use their CI on a daily basis. All three subjects use their CI solely for sound detection and to support their communication via sign language. While one patient expressed disappointment with the poor speech recognition outcome, all three recipients were satisfied with the ability to hear ambient sounds. Two subjects reported increased sense of security and heightened alertness.

Poor Performance in the USH1 Group • Besides the late-implanted USH1 subjects, a phoneme score at 65 dB SPL <70% was observed in one ear (USH1-11.2) of subject USH1-11. A CI was implanted in this subject's left ear at the age of 2 years while she was living abroad. Unfortunately, only limited clinical data of her first years of experience were with her CI were available and therefore this ear was excluded from our analyses. She first visited our clinic at the age of seven, and over the years, phoneme scores between 95 and 100% at 65 SPL were measured with her first CI. She never used a hearing aid for her right ear. At the age of eight, she received a second CI in her right ear but struggled to get used to the sound of this second CI. As a result, she became a nonuser for this ear.

Simultaneous Versus Sequential Implantation in USH1 • In the entire USH1 group, 10 subjects underwent bilateral cochlear implantation, all of whom were implanted during childhood at a median age of 12 months (IQR = 11 to 16). Among these, seven were simultaneously implanted (73.7%), while the remaining three underwent sequential implantation (26.3%).

To evaluate outcomes between simultaneous and sequential implantation, binaural-aided phoneme scores at 65 dB SPL were compared. Subject USH1-11 was excluded from this analysis because no binaural-aided phoneme scores were measured in this subject. Consequently, only two subjects were included in the sequentially implanted group. At 5.3 ± 1.7 years after simultaneous or sequential implantation, the binaural aided phoneme score at 65 dB SPL was significantly higher

TABLE 3. USH-gene variants in the study population

Gene	NM Number	cDNA Variant	Protein Variant	Type of Mutation	Classification	N	%
ADGRV1	NM_032119.4	c.8875C>T	p.(Arg2959*)	Truncating	Pathogenic	4	5, 6
CDH23	NM_022124.6	c.3706C>T	p.(Arg1236*)	Truncating	Pathogenic	1	1, 4
CDH23	NM_022124.6	c.3955G>T	p.(Glu1319*)	Truncating	Pathogenic	1	1, 4
CDH23	NM_022124.6	c.6050-9G>A	r.6049_6050insGTGCCAG p.(Val2018fs)	Truncating	Pathogenic	3	4, 2
CLRN1	NM_174878.3	c.149_152delins7	p.(Ser50fs)	Truncating	Pathogenic	7	9, 7
CLRN1	NM_174878.3	c.528T>G	p.(Tyr176*)	Truncating	Pathogenic	1	1, 4
MYO7A	NM_000260.4	c.1522T>C	p.(Ser508Pro)	Missense	Likely pathogenic	2	2, 8
MYO7A	NM_000260.4	c.1849T>C	p.(Ser617Pro)	Missense	Pathogenic	1	1, 4
MYO7A	NM_000260.4	c.2078del	p.(Lys693fs)	Truncating	Likely pathogenic	2	2, 8
MYO7A	NM_000260.4	c.3039dup	p.(Thr1014fs)	Truncating	Likely pathogenic	2	2, 8
MYO7A	NM_000260.4	c.3109-2A>G	r.spl	Splice	Pathogenic	1	1, 4
MYO7A	NM_000260.4	c.3508G>A	p.(Glu1170Lys)	Missense	Pathogenic	2	2, 8
MYO7A	NM_000260.4	c.3719G>A	p.(Arg1240Gln)	Missense	Pathogenic	3	4, 2
MYO7A	NM_000260.4	c.3764del	p.(Lys1255fs)	Truncating	Pathogenic	1	1, 4
MYO7A	NM_000260.4	c.4117C>T	p.(Arg1373*)	Truncating	Pathogenic	1	1, 4
MYO7A	NM_000260.4	c.5392C>T	p.(Gln1798*)	Truncating	Pathogenic	1	1, 4
MYO7A	NM_000260.4	c.5573T>C	p.(Leu1858Pro)	Missense	Pathogenic	1	1, 4
MYO7A	NM_000260.4	c.5648G>A	p.(Arg1883Gln)	Missense	Pathogenic	1	1, 4
MYO7A	NM_000260.4	c.5944G>A	r.5857_5944del p.(Val1953fs)	Splice	Pathogenic	1	1, 4
MYO7A	NM_000260.4	c.6028G>A	p.(Asp2010Asn)	Missense	Pathogenic	1	1, 4
MYO7A	NM_000260.4	c.6598C>T	p.(Gln2200*)	Truncating	VUS	1	1, 4
PCDH15	NM_001142769.2	c.4542dup	p.(Pro1515fs)	Truncating	Likely pathogenic	2	2, 8
USH1C	NM_153676.4	c.364C>T	p.(Gln122*)	Truncating	Pathogenic	2	2, 8
USH2A	NM_206933.4	c.949C>A	r.951_1143del p.(Tyr318fs)	Missense	Pathogenic	2	2, 8
USH2A	NM_206933.4	c.10525A>T	p.(Lys3509*)	Truncating	Pathogenic	1	1, 4
USH2A	NM_206933.4	c.11864G>A	p.(Trp3955*)	Truncating	Pathogenic	2	2, 8
USH2A	NM_206933.4	c.1256G>T	p.(Cys419Phe)	Missense	Pathogenic	5	6, 9
USH2A	NM_206933.4	c.14583-20C>T	r.spl?	Splice	VUS	1	1, 4
USH2A	NM_206933.4	c.14289del	p.(Ile4764fs)	Truncating	Pathogenic	1	1, 4
USH2A	NM_206933.4	c.1606T>C	p.(Cys536Arg)	Missense	Pathogenic	2	2, 8
USH2A	NM_206933.4	c.2276G>T	p.(Cys759Phe)	Missense	Pathogenic	1	1, 4
USH2A	NM_206933.4	c.2299del	p.(Glu767fs)	Truncating	Pathogenic	6	8, 3
USH2A	NM_206933.4	c.5018T>C	p.(Leu1673Pro)	Missense	Pathogenic	3	4, 2
USH2A	NM_206933.4	c.5907C>A	p.(Tyr1969*)	Truncating	Pathogenic	1	1, 4
USH2A	NM_206933.4	c.6325+1G>C	r.spl	Splice	Pathogenic	1	1, 4
USH2A	NM_206933.4	c.7121-8313_11048-962delins12	p.(Val2374_Gly3683del)	Truncating	Pathogenic	1	1, 4
USH2A	NM_206933.4	c.8079G>A	p.(Trp2693*)	Truncating	Pathogenic	2	2, 8
USH2A	NM_206933.4	c.8723_8724del	p.(Val2908fs)	Truncating	Pathogenic	1	1, 4

in the simultaneously implanted subjects (N = 7, median phoneme score = 98% [IQR = 96 to 100]) compared with the sequentially implanted subjects (N = 2, median phoneme score = 92%, $p = 0.028$). There was no significant difference in the age of implantation between the two groups ($p = 0.197$).

USH Type 2

Cochlear implantation was performed in the subgroup of subjects with USH2 (N = 17) in 23 ears at a median age of 53 (IQR = 42 to 63) years. Six subjects received sequential bilateral implants. A total of 22 ears (95.7%) were rehabilitated with hearing aids before cochlear implantation. The preoperative unaided $PTA_{0,5\text{-}4kHz}$ was 100 ± 12 dB HL (N = 23 ears), while the preoperative best-aided $PTA_{0,5\text{-}4kHz}$ was 53 ± 15 dB HL (N = 23 ears). The latter significantly improved with CI to 27 ± 3 dB HL postimplantation ($p < 0.001$; N = 22 ears) and remained stable over time (Fig. 2A1). The median best-aided preoperative phoneme score at 65 dB SPL was 50% (IQR = 12 to 57; N = 21 ears). With a mean follow-up time of 14 ± 3 months postimplantation, the median phoneme scores significantly increased to 86% (IQR = 79 to 95; $p < 0.001$; N = 21 ears). This value remained stable after a mean follow-up of 4.8 ± 2.8 years with 90% (IQR = 81 to 95; $p = 0.245$, N = 16 ears), and 7.9 ± 2.9 years with 85% (IQR = 81 to 95; $p = 0.344$, N = 7 ears; Figs. 2A2, A3).

Poor Performance in the USH2 Group • A phoneme score of <70% at 65 dB SPL was observed in two subjects. Subject USH2-4 was implanted sequentially at 62 and 64 years. Initially, this subject had an adequate phoneme score of 73%, 18 months after implantation of the first CI. After this subject received a

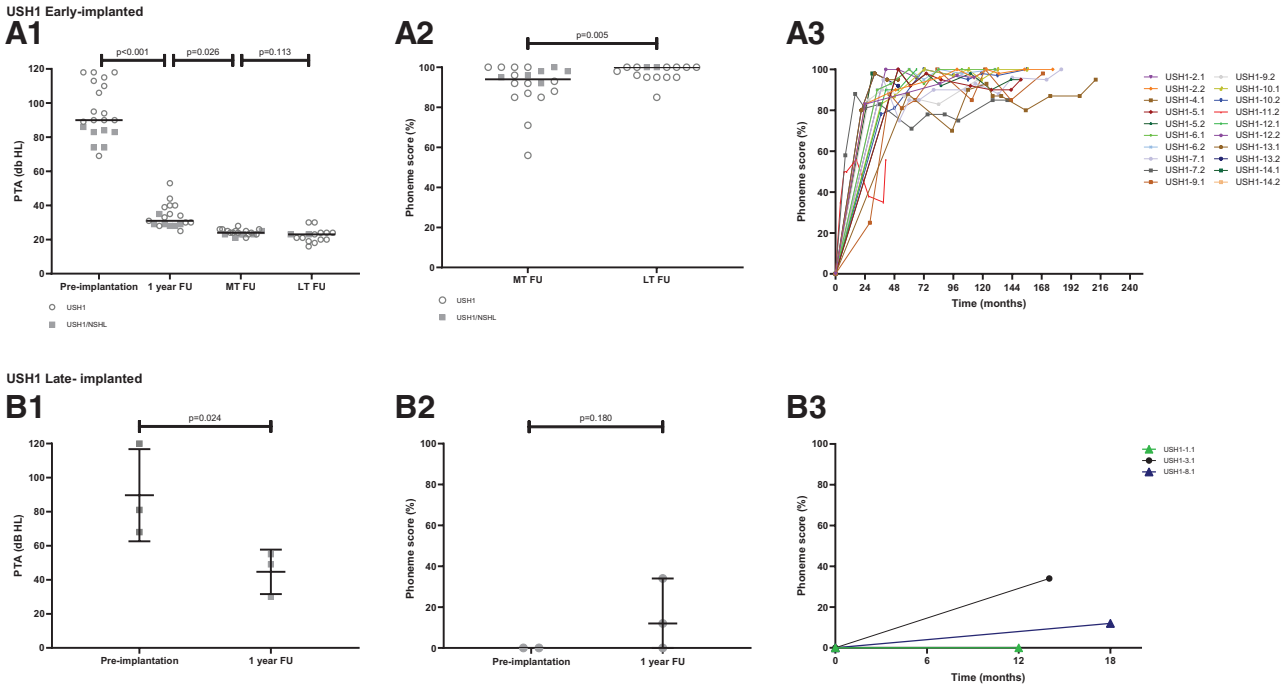

Fig. 1. Cochlear implant performance in subjects with USH1. FU indicates follow-up; LT, long-term; MT, middle-term; NSHL, nonsyndromic hearing loss; PTA indicates pure-tone average; USH1, Usher syndrome type 1. Row A represents the early-implanted USH1 subjects, and row B represents late-implanted subjects with USH1. In the early-implanted USH1 group, circles represent subjects diagnosed with USH1, while squares represent subjects who could not yet be diagnosed with either USH1 or nonsyndromic hearing loss. The preimplantation PTA indicates the best-aided/unaided $_{PTA0,5\text{-}4kHz}$ measured with inserts/headphones. The follow-up $PTA_{0,5\text{-}4kHz}$ are free field measurements. Phoneme scores were measured at 65 dB SPL in quiet. A1, Individual scores with grand mean of $PTA_{0,5\text{-}4kHz}$ scores in the early-implanted USH1 group. The MT FU was 4.5 ± 1.3 yrs; LT FU was 12.0 ± 3.3 yrs. A2, Individual scores with grand median of phoneme scores 65 dB SPL in quiet in the early-implanted USH1 group. There were no preimplantation and 1-yr FU available; MT FU was 4.8 ± 0.9 yrs, LT FU was 11.8 ± 3.3 yrs. A3, Phoneme score at 65 dB SPL in quiet of each ear in the early-implanted USH1 group over the years. B1, Individual scores with mean ± SD of $PTA_{0,5\text{-}4kHz}$ scores in the late-implanted USH1 group. The 1-yr FU was 14 ± 3.5 mos; MT and LT FU were not available. B2, Individual scores with median and IQR of phoneme scores at 65 dB SPL in quiet in the early-implanted USH1 group. The 1-yr FU was 15 ± 3 mos; MT and LT FU were not available. B3, Phoneme score at 65 dB SPL of each ear in the late-implanted USH1 group over time.

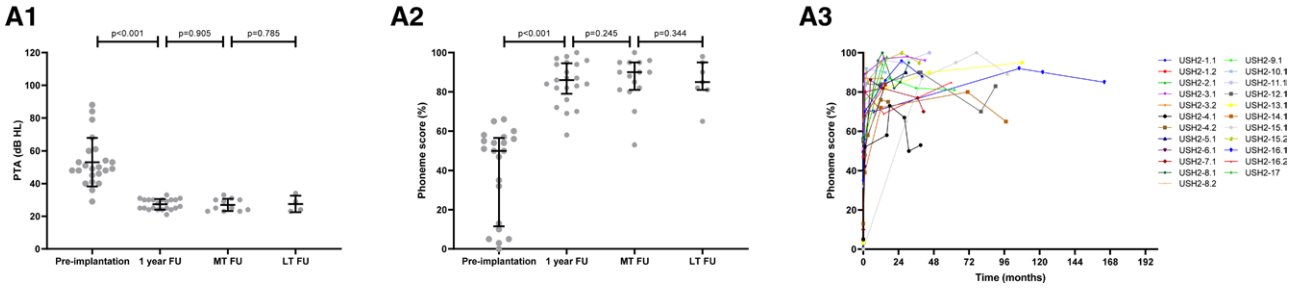

Fig. 2. Cochlear implant performance in subjects with USH2. FU indicates follow-up; LT, long-term; MT, middle-term; PTA, pure-tone average. A1, Individual scores with mean ± SD of $PTA_{0,5\text{-}4kHz}$ scores in the USH2 group. The 1-yr FU was 14 ± 3 mos; MT FU was 4.3 ± 2.3 yrs, LT FU was 8.1 ± 1.4 yrs. A2, Individual scores with median and IQR of phoneme scores at 65 dB SPL in quiet in the USH2 group. The 1-yr FU was 14 ± 3 mos; MT FU was 4.8 ± 2.8 yrs, LT FU was 7.9 ± 2.9 yrs. A3, Phoneme score at 65 dB SPL in quiet of each ear in the USH2 group over the years.

second CI in the contralateral ear, this CI dominated the first CI. As a consequence, the subject limited using the first CI, leading to a decrease in phoneme scores over time, dropping to 53%. No explanation for this phenomenon could be found.

Subject USH2-14 received a CI at the age of 65 years. This subject initially had adequate phoneme scores of 72% and 80%, 1 and 6 years postimplantation. At 8 years postimplantation, the phoneme score decreased to 65%. However, this last measurement may be less reliable because the subject reported being tired that day. Also, some signs of cognitive decline were observed. Nevertheless, when the phoneme score was measured with CI and hearing aid together, she still scored 75%.

USH Type 3

Cochlear implantation was performed in seven ears in the subgroup of four subjects with USH3 with a mean age at

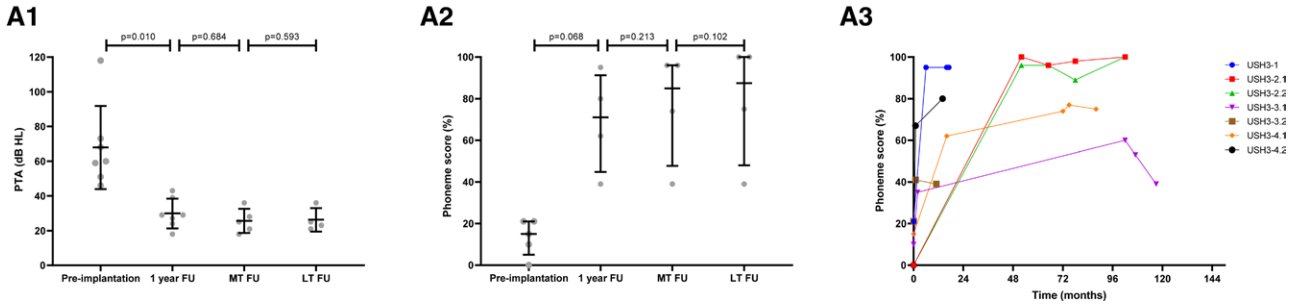

Fig. 3. Cochlear implant performance in subjects with USH3. FU indicates follow-up; LT, long-term; MT, middle-term; PTA, pure-tone average. A1, Individual scores with mean ± SD of $PTA_{0,5\text{-}4kHz}$ scores in the USH3 group. The 1-yr FU was 16 ± 5 mos; MT FU was 5.6 ± 2.5 yrs, LT FU was 8.3 ± 0.6 yrs. A2, Individual scores with median and IQR of phoneme scores at 65 dB SPL in quiet in the USH3 group. The 1-yr FU was 13 ± 8 mos; MT FU was 6.7 ± 2.1 yrs, LT FU was 8.5 ± 1.0 yrs. A3, Phoneme score at 65 dB SPL in quiet of each ear in the USH3 group over the years.

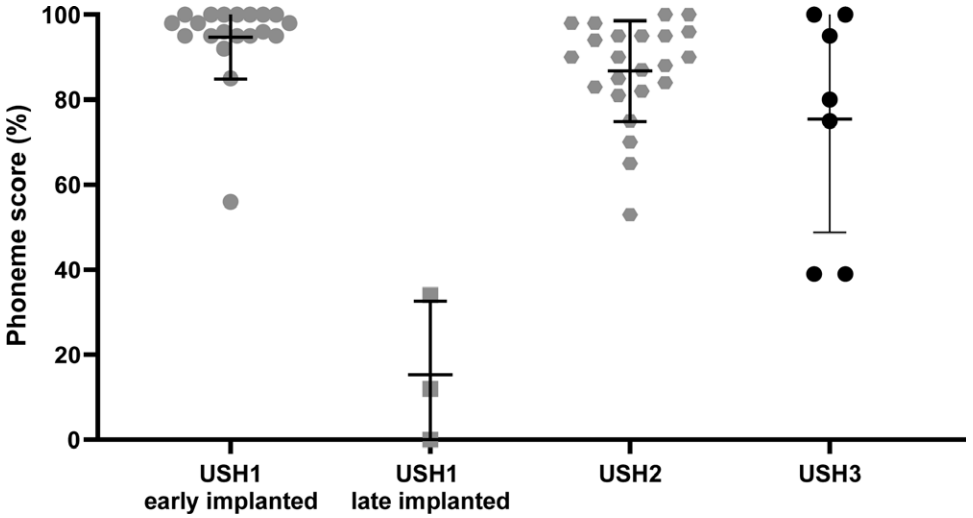

Fig. 4. Phoneme scores in total study population. Individual scores with median and IQR of the last measured phoneme scores at 65 dB SPL in quiet in the four subgroups, including early implanted USH, late-implanted USH1, USH2, and USH3. The overall follow-up was 6.1 ± 4.8 yrs.

implantation of 35 ± 25 years. Six ears (86%) were rehabilitated with hearing aids before implantation. The preoperative unaided $PTA_{0,5\text{-}4kHz}$ was 108 ± 6 dB HL (N = 7 ears). The preoperative best-aided $PTA_{0,5\text{-}4kHz}$ was 68 ± 24 dB HL (N = 7 ears) and significantly decreased to 30 ± 9 dB HL (N = 7 ears) at 16 ± 5 months postimplantation (p = 0.010). This value remained stable over time (Fig. 3A1). The median best-aided preoperative phoneme score at 65 dB SPL in quiet was 15% (IQR = 5.0 to 21; N = 5 ears). This score increased to 71% (IQR = 45 to 91) at 14 ± 2 months postimplantation (p = 0.068), after which this score remained stable over the years (Figs. 3A2, A3).

Poor Performance in the USH3 Group • A phoneme score at 65 dB SPL <70% was found bilaterally in one subject (USH3-3), who was sequentially implanted at the age of 31 and 39 years. The preimplantation MRI showed bilateral hypoplasia of the cochlear nerve. Although in both ears a phoneme score of 39% was found, she can adequately converse in a dialogue. At the same time, she does experience difficulties conversing in a larger group or a noisy environment.

Phoneme Scores in the Total Study Population

Figure 4 shows the long-term phoneme scores for the entire study group. Performance with CIs, in general, is excellent. A comparison of speech recognition scores between the four defined subgroups showed that the late-implanted USH1 group scored significantly lower ($p < 0.001$) compared with the early implanted USH1 group, USH2 group, and USH3 group (Fig. 4). Over the long-term, early implanted USH1 subjects perform significantly better than the USH2 group (p = 0.002), while there was no difference in speech recognition scores between the USH2 and USH3 group (p = 0.539), and the early implanted USH1 and USH3 group (p = 0.094).

Timing of Cochlear Implantation

In the early implanted USH1 group, a younger age at implantation was significantly associated with higher postoperative phoneme scores (R^2 = 0.871, $p < 0.001$, Supplementary Figure 1A in Supplemental Digital Content, http://links.lww.com/EANDH/B444). While correcting for potential confounders, including the degree of hearing loss preimplantation (i.e., unaided PTA 0, 5 to 4 kHz) and self-reported duration of SNHL, the age at implantation accounted for 88.8% variance in speech recognition outcomes ($p < 0.001$, VIFs ≤1.3).

In the USH2 group, a younger age at implantation was also associated with higher speech recognition scores (R^2 = 0.281, p = 0.042, Supplementary Figure 1B in Supplemental Digital

Content, http://links.lww.com/EANDH/B444). After correcting for confounding variables (the degree of hearing loss preimplantation (i.e., unaided $PTA_{0,5\text{-}4kHz}$), and use of hearing-aid preimplantation), this correlation was no longer significant ($R^2 = 0.120$, $p = 0.253$, VIFs ≤1.1). The self-reported duration of SNHL was excluded as a confounder from this multiple regression analysis due to collinearity with the age at implantation (VIF = 12.6).

Aided speech recognition scores before implantation were found to be predictive of postimplantation outcomes ($R^2 = 0.362$, $p = 0.038$) in the USH2 group. After correcting for confounders (i.e., the degree of hearing loss preimplantation (unaided $PTA_{0,5\text{-}4kHz}$), age at implantation, and use of hearing-aid preimplantation; all VIFs <2.4), this correlation was no longer significant ($R^2 = 0.157$, $p = 0.297$). So, while a younger age at implantation appears to be associated with higher phoneme scores after implantation, other factors, like auditory stimulation, diminish the effect of the age of implantation. This implies that the significance of the age at which implantation occurs diminishes when consistent auditory stimulation is provided.

There were too few USH3 subjects to assess the timing of implantation in this subgroup properly.

DISCUSSION

This study aimed to evaluate long-term CI performance in CI recipients with all types of USH, at both short-term and long-term, considering each subtype separately. Overall, we found excellent long-term outcomes, especially in early implanted USH1 subjects and USH2 and USH3 recipients. Late-implanted subjects with USH1, however, showed poor outcomes regarding speech recognition but indicated a clear benefit from CI in sound localization and sound awareness.

USH Type 1

Subjects with USH1 have congenital, profound, bilateral SNHL and are therefore ideal candidates for early implantation. Almost all early implanted USH1-recipients in this study had excellent CI outcomes, which is in line with multiple previous studies (Loundon et al. 2003; Pennings et al. 2006; Davies et al. 2021; Remjasz-Jurek et al. 2023). In addition, we found that simultaneously implanted subjects had significantly better outcomes than sequentially implanted individuals. Furthermore, one out of three sequential CI recipients had difficulties adjusting to the second CI and had poorer outcomes (i.e., a phoneme score <70% at 65 dB SPL with the second CI). This poor performer received her second CI 6 years after the first one at the age of eight and only used it for sound detection. Previous studies reported better auditory outcomes following early and bilateral CI in subjects with USH1 (Jatana et al. 2013; Davies et al. 2021) and found that simultaneous implantation is preferred over sequential CI in prelingual SNHL (Chadha et al. 2011; Elrashidy et al. 2020). Notably, children receiving CI at 6 months of age achieve even better long-term outcomes than those implanted at 12 months (Ching et al. 2017).

In addition, central and peripheral nerve system changes due to auditory deprivation can be restored to near-normal till the age of 3.5 to 4.0 years. This central auditory system plasticity remains in some children until approximately seven years of age. After this age, central auditory system plasticity is greatly reduced, and poorer outcomes are to be expected (Sharma et al. 2002; Kral & Sharma 2012). This factor probably explains why the subject who received the second implant at the age of eight had poorer outcomes because she never used a hearing aid in this ear. Taken together, our data, in line with previous studies, indicate that the best outcomes for USH1 subjects are achieved by early simultaneous implantation.

Three USH1 subjects in this study received a CI during adulthood. Sound detection could be achieved in all recipients, but speech recognition was insufficient for oral communication, which is in line with previous research (Hoshino et al. 2017). In addition, a recent systematic review evaluating CI outcomes in early deafened late-implanted adults found postoperative phoneme scores between 20 and 49% (Debruyne et al. 2020). Although this is higher than the median phoneme score of 12% found in our late-implanted USH1 subjects, these phoneme scores are likely insufficient for oral communication. Lower speech recognition scores in late-implanted USH1 subjects are probably linked to the long-term absence of auditory stimulation resulting in profound changes in the structure and function of the central auditory system (Syka 2002).

Moreover, late-implanted USH1 subjects have not acquired spoken language. As a result, developing speech understanding postimplantation is challenging. In addition, SNHL can be accompanied by degeneration of SGNs (Nadol et al. 2001; Nadol & Eddington 2006) and because CI directly stimulates SGNs, (secondary) degeneration may also negatively influence CI performance (Eppsteiner et al. 2012).

So, even though the late-implanted USH1 subjects in our study are not able to communicate with a CI, they were all satisfied with being able to hear sound. This made them feel more alert, safer, and more connected to the world. Moreover, using hearing-related questionnaires, such as the Nijmegen Cochlear Implant Questionnaire, subjects have shown significant improvements postimplantation in early deafened late-implanted adults (Damen et al. 2006; Debruyne et al. 2020). This indicates that CI can also be valuable in this population in terms of quality of life, even when speech perception is poor. So it is crucial to highlight during preimplantation counseling that CI is unlikely to result in significant improvements in speech recognition in this specific group. Instead, the primary function of a CI is to act as a signaling device.

USH Type 2

Progressive hearing loss in USH2 might lead to insufficient speech recognition, with hearing aids increasing the eligibility for CI in these subjects. Although USH2 is the most common subtype of USH, CI outcomes in this population have been studied only to a limited extent. Hartel et al. (2017) evaluated CI performance in subjects with USH2A and found significantly improved speech recognition with a mean postimplantation phoneme score of 87%. This is in line with the phoneme scores found in our study population. It should be noted, however, that there is some overlap of implanted subjects in the study populations. A couple of other studies evaluated outcomes following cochlear implantation in study populations that included subjects with USH2, but none of these outcomes were exclusively based on subjects with USH2 (Jatana et al. 2013; Alzhrani et al. 2018; Remjasz-Jurek et al. 2023).

In this study, we found good and stable outcomes following CI in subjects with USH2. Only two subjects who were implanted later in life showed a decline in performance over the years, possibly caused by a combination of factors, including a decline in cognitive performance (Blamey et al. 2013). In addition, we also observed a trend in our results where individuals who were implanted later and those with a lower preimplantation aided speech perception score showed less beneficial outcomes after implantation. Both factors (age and preimplantation performance) have previously been shown to result in poorer outcomes in CI recipients in a general population (Holden et al. 2013; Hoppe et al. 2019). This implies that cochlear implantation should be considered early in USH2 subjects with insufficient speech recognition with hearing aids, especially in combination with severe visual impairment.

USH Type 3

In subjects with USH3, the degree of hearing loss is highly variable (Plantinga et al. 2005). This means that USH3 subjects receive a CI at widely varying ages. Pietola et al. (2012) evaluated speech recognition 1 year postimplantation in a Finnish cohort of USH3 subjects (N = 19 subjects) with the same founder mutation. Despite this genetically homogeneous group, the age at implantation varied significantly. An overall beneficial outcome was reported following cochlear implantation. However, a substantial variation in speech recognition scores was found (Pietola et al. 2012). While the underlying factors leading to the broad phenotype in USH3 are unknown, Pietola et al. (2012) suggested that the effects of alternative splicing or modifier genes might be involved in the varied phenotype and CI performance. Although not specifically assessed, CI performance in their population might also be influenced by known factors attributing to CI performance, such as the duration of SNHL, age of onset of SNHL, and duration of CI experience (Blamey et al. 2013).

In our study, we also found a wide range in both the age at implantation and postimplantation phoneme scores. Although evaluated in a smaller population (N = 4 subjects), we found higher phoneme scores compared with the Finnish study (71% [IQR = 45 to 91] versus 52% ± 33%). Only one subject (implanted bilaterally) demonstrated low phoneme scores in both ears, attributed to bilateral hypoplasia of the cochlear nerve. This finding is crucial, highlighting that individuals with a hypoplastic auditory nerve may benefit less from CIs. The reduced nerve fibers could impair the transmission of electrically evoked signals from the implant to the brain. Furthermore, previous studies showed poorer CI outcomes in recipients with cochlear nerve deficiency compared with recipients with normal cochlear nerve (Kang et al. 2010; Buchman et al. 2011; Kutz et al. 2011; Vesseur et al. 2018). Overall, individuals with USH3 benefit from CI, but preimplantation counseling should highlight the considerable variability in outcomes.

CI Performance in USH

When comparing CI performance across the three subtypes, overall good performance was observed in the early implanted USH1 group, USH2 group, and USH3 group, while the late-implanted USH1 group scored significantly lower phoneme scores. In addition, early implanted USH1 subjects showed better outcomes than the USH2 and USH3 groups. In general, subjects with USH2 and USH3 have a longer self-reported duration of SNHL and an older age during implantation. Both of these factors correlate with lower CI performance (Blamey et al. 2013; Holden et al. 2013). Nevertheless, our findings suggest that individuals with USH2 should be implanted while having adequate speech recognition using HA. Prolonged inadequacy in speech recognition may have adverse effects on CI performance. The recommendation to keep using hearing aids and consider early implantation also applies to USH3 subjects.

It is interesting that *USH2A* and *CLRN1* are not only involved in hair cell development, but their encoded proteins are also reported to be a component of the synaptic complexes (Reiners et al. 2005; Zallocchi et al. 2009; Dulon et al. 2018). According to the spiral ganglion hypothesis proposed by Eppsteiner et al. (2012), poorer CI performance is expected when the SGNs and/or auditory nerves degenerate over time, while good performance is anticipated when only the hair cells are affected. However, our findings, showing good and stable long-term CI outcomes in subjects with USH2 and USH3, contradict this hypothesis. This suggests that either *USH2A's* and *CLRN1's* involvement in SGN may not be as significant or that the spiral ganglion hypothesis is incorrect. Future studies are needed in genotyped CI recipients with affected genes that are mainly expressed in the SGN to confirm or refute this hypothesis.

Strengths and Limitations

This study is currently one of the largest and most comprehensive studies evaluating CI outcomes in individuals with USH in both the short- and long-term, considering each subtype separately.

The primary limitation of this study was the small sample size in specific subgroups. Given the significant variability in phenotype among the three USH subtypes, we opted to assess CI performance separately in each subtype, resulting in smaller sample sizes, particularly in the late-implanted USH1 group and USH3 group. Subsequently, statistical testing in these subgroups has limited value. Although the observed CI outcomes in these groups align with prior research (Pietola et al. 2012; Hoshino et al. 2017), they should be interpreted cautiously. Furthermore, the analysis comparing CI outcomes between simultaneous and sequential implanted USH1 individuals included a limited number of subjects (seven and two, respectively). Although this analysis indicated that simultaneous implantation resulted in significantly better outcomes, the statistical testing has limited value due to the small sample size. Nevertheless, this finding is consistent with previous research (Chadha et al. 2011; Elrashidy et al. 2020). Second, this study was limited by its retrospective design, which inevitably resulted in some missing data.

Conclusion and Clinical Implications

This study found that most individuals with USH have beneficial outcomes following cochlear implantation, both long- and short-term. The best CI outcomes in USH1 subjects are expected following early simultaneous bilateral implantation before the age of 8 years, but preferably at the age of 6 months (Ching et al. 2017). Late implantation in USH1 subjects might be considered. However, in these subjects, the CI will mainly have a signaling function, and in most cases, speech recognition

scores will be insufficient for oral communication. This must be adequately explained to adult USH1 subjects considering CI.

In individuals with USH2 and USH3, beneficial outcomes are anticipated following CI, particularly in those who have sufficient speech recognition with their hearing aids and have received sufficient auditory stimulation before implantation. In subjects with USH2, cochlear implantation should be considered earlier than in participants without visual impairment. In individuals with USH3, however, it is more challenging to predict postimplantation outcomes due to the wide variability in CI performance within this group. Therefore, counseling for individuals with USH2 and USH3 should emphasize the benefit of early implantation and stimulate the use of HA, even if individuals perceive minimal to no benefit. The findings of this study can be used for preimplantation counseling and expectation management for individuals with USH who consider CI.

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