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COCHLEAR IMPLANTATION IN CHILDREN WITH ENLARGED VESTIBULAR AQUEDUCT (EVA): RELATIONSHIP TO PENDRED SYNDROME DIAGNOSIS, SURGICAL OUTCOMES, AND RADIOLOGICAL FINDINGS

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Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

Abstract

Introduction: The cochlear implant (CI) procedure in patients with inner ear malformations is challenging. The aim of this study was to evaluate auditory perception and speech development in children with enlarged vestibular aqueduct (EVA) and to relate the results to the diagnosis of Pendred syndrome (PS), imaging findings, surgical course, and postoperative period.

Material and methods: The study group consisted of 49 children with EVA, aged 11 months to 15 years, with severe to profound hearing loss. The EVA patients included 22 with PS and 27 with nonsyndromic EVA (NSEVA). The control group consisted of 46 children with nonsyndromic deafness. Outcomes after cochlear implantation were evaluated annually for at least 10 years. Auditory performance was assessed by categories of auditory performance (CAP) and Meaningful Auditory Integration Scale (MAIS). Speech outcomes were evaluated by Speech Intelligibility Rating Scale (SIR) and Meaning Use of Speech Scale (MUSS). Genetic counselling, imaging studies, and vestibular testing were also evaluated when available.

Results: All patients included in the study benefited from cochlear implants, especially when implantation was performed before the age of 3 years. After CI, EVA patients (PS and NSEVA) achieved a steeper rate of increase in auditory perception and speech intelligibility, demonstrating higher scores at each follow-up point compared to nonsyndromic patients (NS). There were no differences in auditory and speech perception between NSEVA and PS patients. In addition to EVA, the most commonly diagnosed malformation was incomplete partition type 2 (IP-2), the presence of which negatively affected postoperative outcomes. During cochleostomy, cerebrospinal fluid (CSF)/perilymph leakage was observed in 50% of implanted ears, but its presence did not affect the final outcomes.

Conclusions: Early cochlear implantation is associated with satisfactory speech and auditory development in children with EVA. Due to the presence of inner ear malformations in patients with Pendred syndrome, detailed imaging of the temporal bone is indicated. Despite the frequent occurrence of CSF/perilymph leakage during cochleostomy, patients with EVA benefit satisfactorily from cochlear implantation.

Key words: hearing loss • EVA • cochlear implantation • Pendred syndrome • inner ear malformation • enlarged vestibular aqueduct

PROCEDURA WSZCZEPIANIA IMPLANTÓW ŚLIMAKOWYCH U DZIECI Z POSZERZONYM WODOCIĄGIEM PRZEDSIONKA (EVA): ZWIĄZEK Z ROZPOZNANIEM ZESPOŁU PENDREDA, PRZEBIEGIEM LECZENIA CHIRURGICZNEGO I WYNIKAMI BADAŃ RADIOLOGICZNYCH

Streszczenie

Wprowadzenie: Procedura wszczepiania implantów ślimakowych (CI) u pacjentów z wadami rozwojowymi ucha wewnętrznego stanowi wyzwanie. Celem tego badania była ocena percepcji słuchu i rozwoju mowy u dzieci z poszerzonym wodociągiem przedsionka (EVA) oraz odniesienie wyników do rozpoznania zespołu Pendreda (PS), a także do wyników badań obrazowych, przebiegu operacji i okresu pooperacyjnego.

Materiał i metody: Grupę badaną stanowiło 49 dzieci z EVA, w wieku od 11 miesięcy do 15 lat, z niedosłuchem od znacznego do głębokiego stopnia. Wśród pacjentów z EVA było 22 z PS i 27 z izolowaną wadą EVA. Grupę kontrolną stanowiło 46 dzieci z głuchotą niesyndromiczną. Wyniki po wszczepieniu implantu ślimakowego były oceniane corocznie przez co najmniej 10 lat. Percepcję słuchu oceniono za pomocą kategorii wydajności słuchowej (CAP) i Skali Słyszenia i Rozumienia Dźwięków. Jakość mowy oceniono z wykorzystaniem skal: Oceny Zrozumiałości Mowy (SIR) i Użycia Mowy do Komunikacji (MUSS). W miarę dostępności oceniono również wyniki badań genetycznych i obrazowych oraz stan narządu przedsionkowego.

Wyniki: Wszyscy pacjenci włączeni do badaniem odnieśli korzyści z implantów ślimakowych, zwłaszcza gdy implantacja została przeprowadzona przed ukończeniem 3 roku życia. Po wszczepieniu implantu pacjenci z EVA (PS i NSEVA) osiągnęli szybszy wzrost percepcji słuchowej i zrozumiałości mowy, wykazując również wyższe wyniki w każdym punkcie obserwacji w porównaniu z pacjentami niesyndromicznymi (NS). Nie odnotowano różnic w zakresie percepcji słuchu i mowy pomiędzy pacjentami z NSEVA i PS. Najczęściej diagnozowaną wadą rozwojową oprócz EVA był niepełny podział typu 2 (IP-2), którego obecność negatywnie wpływała na pooperacyjne wyniki. Podczas kochleostomii wyciek płynu mózgowo-rdzeniowego/perylimfy zaobserwowano w 50% implantowanych uszach, ale jego obecność nie miała wpływu na ostateczne wyniki leczenia

Wnioski: Wczesne wszczepienie implantu ślimakowego wiąże się z zadowalającym poziomem rozwoju mowy i słuchu u dzieci z EVA. Ze względu na obecność wad rozwojowych ucha wewnętrznego u pacjentów z zespołem Pendreda, wskazane jest szczegółowe obrazowanie kości skroniowej. Pomimo częstego występowania wycieku płynu mózgowo-rdzeniowego/perylimfy podczas wykonywania kochleostomii, u pacjentów z EVA, odnoszą oni zadowalające korzyści z implantacji ślimakowej.

Słowa kluczowe: niedosłuch • EVA • implantacja ślimakowa • zespół Pendreda • wady rozwojowe ucha wewnętrznego • poszerzony wodociąg przedsionka

Key for abbreviation	
ABR	auditory brainstem response
ADHD	attention deficit hyperactivity disorder
BOR	branchio-oto-renal syndrome
CAP	categories of auditory performance
CDC	Centers for Disease Control and Prevention
CI	cochlear implantation
CMV	*Cytomegalovirus*
CSF	cerebrospinal fluid
CT	computed tomography
dRTA	distal renal tubular acidosis
EEABR	electrically evoked auditory brainstem response
EVA	enlarged vestibular aqueduct
HAs	hearing aids
HIV	human immunodeficiency virus
HL	hearing loss
HRCT	high-resolution computed tomography
HSV	*Herpes simplex* virus
HT	head trauma
IEM	inner ear malformation
IP-2	incomplete partition type 2
IQ	intelligence quotient
IT-MAIS	Infant-Toddler Meaningful Auditory Integration Scale
MAIS	Meaningful Auditory Integration Scale
MRI	magnetic resonance imaging
MUSS	Meaningful Use of Speech Scale
NS	nonsyndromic patients
NSEVA	Nonsyndromic EVA
PDT	perchlorate discharge test
PS	Pendred syndrome
PTA	pure tone audiometry
SIR	speech intelligibility rating
SNHL	sensorineural hearing loss
SNK	Student–Newman–Keuls test
VNG	videonystagmography
VZV	*Varicella zoster* virus

Introduction

According to research, congenital sensorineural hearing loss (SNHL) in children may be attributed to inner ear malformations, which are associated with approximately 20% of cases [1]. The enlarged vestibular aqueduct (EVA), first identified and described by Valvasorri in 1978 [2], is the most common bony inner ear malformation (IEM) that is demonstrated by computed tomography (CT) [3]. The etiology of congenital significant sensorineural hearing loss (SNHL) has been linked to various factors, including environmental and genetic. Among these factors, EVA has been identified as a causative factor in approximately 10% of cases of significant congenital SNHL [3]. Thus, IEMs are the third leading cause of hearing loss in the pediatric population [4].

Anomalies of the temporal bone pyramid, mainly the EVA, may manifest as an isolated (nonsyndromic) disorder or as part of a constellation of syndromic symptoms associated with specific genetic mutations [4]. It is critical to distinguish between two different conditions related to EVA, including NSEVA, caused by a mutation in the *DFNB4* gene, and Pendred syndrome (PS). These two disorders are associated with a wide range of hearing impairments, vestibular dysfunction, and temporal bone abnormalities. However, PS is predominantly associated with a thyroid iodine-organising defect, leading to the development of goiter and hypothyroidism in the second decade of life. Therefore, it is recommended that patients diagnosed with EVA should undergo routine monitoring for potential thyroid dysfunction [5]. Furthermore, EVA has been observed in several other disorders, including branchio-oto-renal syndrome (BOR), distal renal tubular acidosis (dRTA), Waardenburg syndrome, and Down syndrome [6].

Classically, hearing loss (HL) in EVA patients is bilateral, predominantly affects higher frequencies, and ranges from mild to profound in severity [7,8]. Typically, HL is diagnosed between 3.5 and 5 years of age, but approximately 50% of cases may have a later onset and a progressive nature [9]. The progression may be rapid in early childhood [10] and associated with minor head trauma, infection, or delayed secondary hydrops [11]. Vertigo can precede or accompany fluctuations in hearing [12,13]. The commonly observed low-frequency air-bone gap, in combination with normal tympanometry, may represent a "third window" effect caused by a dilated vestibular aqueduct [14].

About half of the cases with NSEVA/PS have been related to pathogenic sequence variants of the Pendrin gene (*SLC26A4*) as homozygous or compound heterozygous mutations [15,16]. Although most NSEVA/PS patients are diagnosed with a compound heterozygous mutation, individuals have one or no pathogenic *SLC24A4* gene mutations [16]. There have also been reports of mutations in the *FoXi1* gene or the *KCNJ10* gene, with or without mutations in the *SLC26A4* gene. However, these mutations occur in about 1% of patient populations [16]. The pathogenic variant of *SLC26A4* results in abnormal production of the Pendrin protein, which plays the role of a Cl^-/HCO_3^- exchanger, which maintains the endolymph's proper composition [17,18]. Regarding the inner ear, Pendrin is found in the endolymphatic duct, sac, utricle, and saccule. Moreover, the expression of *SLC26A4* in the cochlea has been detected in the external sulcus cells, the spiral ligament, Claudius cells, Deiters cells, and the spiral ganglion of the cochlea [19–21]. Genetic testing may identify patients with NSEVA and PS but may not be sufficient for those with still normally functioning thyroid glands. Therefore, a perchlorate discharge test (PDT), which quantifies the level of radioisotope-labelled iodide secretion by the thyroid gland in response to oral or intravenous administration of perchlorate, helps establish the proper diagnosis. Patients with PS have characteristically high discharge levels, regardless of clinical thyroid status [22].

Since the first successful cochlear implantation in 1995 in a 6-year-old boy with EVA [23], only a few reports are available on the results of patients with this type of IEM. Overall, according to the results of small study populations, cochlear implantation in patients with EVA has been generally beneficial [24,25]. However, due to the abnormal ear anatomy of patients with NSEVA/PS, performing a CI in such patients may predispose them to adverse events such as CSF leakage/gusher, incomplete electrode insertion, or an increased risk of meningitis [24]. The presumed cause of such complications is endolymphatic sac enlargement that leads to abnormal communication with the subarachnoid space in the posterior fossa.

The principles of managing EVA-induced HL have evolved over the years, and cochlear implants are regarded as the gold standard for treating deafness in patients who meet implantation criteria [26,27]. The excellent efficacy of implantation in the youngest patients has already been repeatedly confirmed in various studies [28,29]; however, due to the specific nature of HL, EVA patients pose a challenge to establishing the appropriate timing of implantation. Therefore, it is essential to assess post-implantation performance in different age groups in EVA patients in order to provide appropriate audiological care. This retrospective study also aimed at determining whether, compared to implanted pediatric populations without EVA, long-term CI outcomes differed between children with nonsyndromic EVA and with Pendred syndrome. Moreover, the study evaluates the impact of additional inner ear malformations and gusher on postoperative outcomes. When reviewing the available literature, it is worth noting that only a few studies address the issues mentioned above. Consequently, this analysis contributes original and essential knowledge to the medical community.

Material and methods

Population and study design

This study is a retrospective analysis of the medical records and images of pediatric patients with EVA who underwent cochlear implantation before the age of 18 years. The Institutional Review Board of the Cochlear Implant Center in Barcelona granted ethics approval for this study. All participants and their parents/guardians provided informed consent to participate in the study. Data on medical history, imaging studies, audiological evaluation, intraoperative incidents, and postoperative results were retrieved from patient files. Data on preoperative dizziness and tinnitus were also collected to avoid misinterpretation of these features as new postoperative complications.

The records of 935 implanted patients were analysed, among whom 57 children with EVA were identified. After checking the inclusion and exclusion criteria, 49 patients with EVA were qualified for further analysis. Subsequently, 22 children with confirmed Pendred syndrome and 27 NSEVA patients were separated from this group. The diagnosis of PS was established before the initial presentation in our department, and the complete diagnostic control was already performed by endocrinologists and through past evaluations of their hearing acuity. The results of the patients in the two groups were compared with each other and related to the reference group, which consisted of 46 nonsyndromic children implanted for deafness of unknown origin.

For further analysis, all patients were divided into four groups based on the age when they received their first cochlear implant. Results were compared between the following groups: CAT1 (0–3 years), CAT2 (4–5 years), CAT3 (6–7 years), and CAT4 (8–17 years) at CI surgery. The purpose of separating patients by age was to determine if and how the age of implantation influenced postoperative outcomes.

Before qualifying for a CI, each child underwent imaging studies: high-resolution computed tomography (HRCT) or magnetic resonance imaging (MRI) of the petrous temporal bone to evaluate inner ear structures and vestibular aqueduct size. RadiAnt DICOM Viewer was used to evaluate the imaging studies. The vestibular aqueduct was considered enlarged if its diameter was greater than 1.5 mm at the midpoint between its origin in the vestibule and its end in the posterior fossa (operculum) [3]. If the cochlea had only 1.5 turns instead of the standard 2.5, with coalescence of the apical and middle turn forming a cystic apex, then it was considered abnormal. This type of IEM, known as incomplete partition type 2 (IP-2), is frequently accompanied by an enlarged vestibule and vestibular aqueduct (historically called Mondini anomaly). In a next step, it was evaluated whether the presence of this malformation affected the postoperative outcomes.

An audiologic assessment was used to determine hearing performance and guide auditory rehabilitation after cochlear implantation. The main components of the audiologic evaluation included pure tone average assessment, speech perception testing, and electrophysiologic evaluation. In general, unaided pure tone audiometry was used to assess for SNHL. In addition, an otoacoustic emissions test was performed. The occurrence of normal otoacoustic emissions in patients with SNHL increased the suspicion of auditory neuropathy, a diagnosis which has a significant impact on the methodology of aural rehabilitation and on expected outcomes. Therefore, children with non-cochlear SNHL assessed by acoustic otoacoustic emissions were excluded from the study. Electrophysiologic tests were used to measure audiologic function in young pediatric patients (< 5 years of age) and patients with developmental delays. The electrophysiologic evaluation included auditory brainstem response (ABR) or electrically evoked auditory brainstem response (EEABR). ABR objectively measures the degree of SNHL in pediatric cochlear implant recipients. A curve approximating hearing thresholds was obtained for 0.125 to 8 kHz. All children included in the study underwent behavioral and electrophysiological testing. In cases of exudative otitis media, conservative or surgical treatment was performed prior to the audiologic evaluation. The audiological assessment was completed using behavioral or tonal audiometry with and without hearing aids (HAs) [29]. Patients with SNHL enrolled in the study underwent comprehensive examinations by our qualified CI team and were classified as suitable candidates for cochlear implantation. None of the patients benefited from wearing HAs, and the audiometric tests indicated severe to profound HL in the ear eligible for implantation.

Following CDC recommendations, all patients were vaccinated against pneumococcus to reduce the risk of meningitis [30]. The same qualified ENT specialist carried out the operation. All patients received the CI using the same technique: a posterior transmastoid tympanotomy followed by a cochleostomy under general anesthesia.

Outcomes after cochlear implantation were measured using validated tools designed to evaluate audiological and language skills. Postoperative auditory performance was assessed by the categories of auditory performance (CAP), which incorporates a hierarchical 8-category scale of everyday auditory perception ranging from 0 (no awareness of environmental sounds) to 7 (uses telephone with a known listener) [31]. Speech performance was assessed by using the Speech Intelligibility Rating Scale (SIR), which is a quick general outcome measure of speech intelligibility in real-life scenarios; it uses five categories ranging from 1 (pre-recognisable words in the spoken language) to 5 (connected speech is intelligible to all listeners) [32]. Parent-reported assessment of the development of auditory and speech production behaviors in children was evaluated using the Meaningful Auditory Integration Scale (MAIS) or its infant-toddler equivalent (IT-MAIS) [33] and Meaningful Use of Speech Scale (MUSS) [34]. The MAIS and IT-MAIS questionnaires were used to assess listening skills, including vocalisation behavior, response to sounds, and the ability to understand the meaning of sounds. The possible score for the patient tested ranged from 0 to 40 [33]. The MUSS questionnaire was used to assess language skills in the areas of voice control, the use of language without gestures and signs, and communication strategies in everyday situations. The scale assessed 11 domains related to situations in which the child uses language. The possible score for the tested patient was the sum of the points obtained in each area and ranged from 0 to 44 [34]. Children were evaluated either by the parents or by the speech-language pathologist. All measurements were recorded once before implantation, every 12 months after the procedure for at least 10 years, and then annually. Follow-up ranged from 11.5 to 14.2 years, with a mean of 12.8 years.

Inclusion criteria were as follows: (a) age < 18 years; (b) severe to profound HL (HL at least > 70 dB HL); (c) limited speech understanding with hearing aids; (d) no effect of HL treatment with hearing aids worn for at least 3 months; (e) availability of imaging studies: MRI of the head or HRCT of the temporal bones in the medical record system; (f) availability of questionnaire results (MAIS or IT-MAIS, CAP, and SIR) prior to implantation and every subsequent year of follow-up for at least 10 years; (g) no evidence of inner ear, auditory nerve, or other abnormalities that would preclude cochlear implantation; (h) consent of the child's parents or guardians to participate in long-term follow-up after cochlear implantation; (i) consent of the child's parent or guardian to cochlear implant surgery; (j) consent of a child between the ages of 16 and 18 to undergo surgery; (k) syndromic HL (for study group); and (l) nonsyndromic HL (for the control group).

Exclusion criteria were the following: (a) age ≥18 years; (b) no audiological indication for a CI; (c) SNHL of extracochlear origin; (d) unilateral deafness or asymmetric HL resulting in HL in one ear only; (e) absence or poor quality of available imaging studies; (f) presence of malformations of the inner ear, auditory nerve, temporal bone, or other structures precluding cochlear implantation; (g) maternal

history of infection during pregnancy (e.g., CMV, HSV, HIV, VZV, influenza, rubella, or toxoplasmosis); (h) neurological diseases and conditions (e.g., sudden palsy, multiple sclerosis, adrenoleukodystrophy, ADHD, IQ < 69); (i) general and mental health conditions contraindicated for general anesthesia or surgery; (j) condition following temporal bone surgery that prevents CI, (k) Infrequent or nonexistent use of a speech processor; (l) inability to perform audiological tasks (e.g., non-English or non-Spanish speaking patients); (m) unavailability of results from questionnaires (MAIS or IT-MAIS, MUSS, CAP, and SIR) assessed annually after CI for at least 10 years; (n) unwillingness of the implanted patient or his/her parent/guardian to participate in the study; (o) dependence on stimulants.

Statistical analysis

For statistical analysis, MedCalc 15.8 (MedCalc, Belgium) software was used. We used a D'Agostino–Pearson test to check if the shape of the distribution was similar to a normal distribution. All studied variables had a normal distribution; and so parametric tests were applied. Values of the following parameters: PTA, CAP, SIR, MAIS/IT-MAIS, and MUSS were measured at 12 time-points – before implantation (T0), each year after surgery (T1–T10), and finally at the last available follow-up (Tlast). Repeated measures ANOVA was used to compare group means (grouping variables) where the participants were the same in each group and between groups (within-subject factor and between-subject factors). We then performed repeated measures ANOVA for single groups (within the grouping variable). The average values of analysed tests estimated by the models were presented as means and related to 95% confidence intervals (95% CIs). Differences in the average level of the analysed parameters between two adjacent measurement points for two various groups were estimated using a Student *t*-test for independent samples with Bonferroni correction for multiple comparisons. The differences in mean values of the studied variables were compared between at least three groups of patients using one-way ANOVA with the Student–Newman–Keuls (SNK) post hoc test. A multiple regression model selected factors affecting the results of final postoperative outcomes. A *p*-level below 0.05 was considered statistically significant.

Results

Patients with Pendred syndrome (PS)

The group comprised 22 patients (55% males) with biallelic mutations in the *SLC26A4* gene and a positive PDT test in all cases. Each patient had profound HL at the time of CI eligibility. There were 14 (64%) patients who were diagnosed with progressive HL, and 4 (18%) reported sudden drops in hearing after minor head trauma. The mean PTA before CI was 107.9 dB HL (SD 4.5, range 95–110 dB).

Videonystagmography (VNG) results demonstrated normal vestibular response in 8 children, hyporeflexia in 5, and areflexia in 2 cases. Preoperative MRI of the head or HRCT of the temporal bones indicated that all patients with PS had bilateral EVA and 5 patients had additional cochlear dysplasia equivalent to IP-2. **Figure 1** shows a sample CT scan of the temporal bones of a PS patient

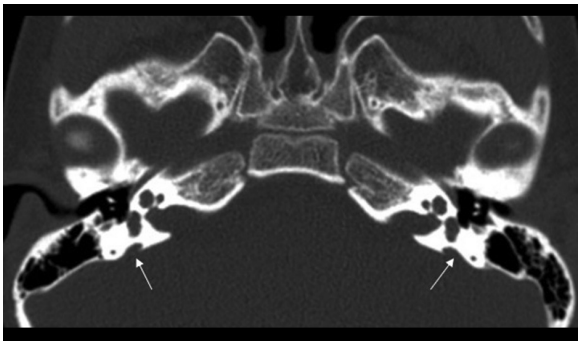

Figure 1. Axial CT image of the temporal bones in a 5-year-old boy with Pendred syndrome; white arrows point to bilaterally enlarged vestibular aqueducts

with bilateral EVA. A thyroid ultrasound revealed no abnormalities in the gland.

The mean age at implantation was 5.8 years (SD 3.9, range 1–13.7 years). There were 10 children who were implanted with Nucleus Freedom implants (Cochlear) and 12 with N24 implants (Cochlear). There were 7 patients who were implanted bilaterally. Of these, 4 received implants simultaneously and 3 sequentially, with implantation of the second ear 6 months after the first. The remaining 15 patients were implanted unilaterally. Despite the abnormal inner ear anatomy, all electrodes were able to be inserted entirely into scala tympani. During cochleostomy, CSF/perilymph leakage was observed in 15 ears (52%) implanted. Of these, a "true gusher" (pulsating outflow over 1 minute) occurred in 6 (21%) ears, but no surgical intervention was needed except for packing with muscle tissue around the electrode.

Transient vertigo (< 24 hours) was the most commonly reported symptom after CI. Other reported postoperative complaints were temporary facial nerve paresis (< 4 weeks), soreness when chewing, or aggravation of existing tinnitus, which are typical of the postoperative period. **Table 1** outlines the specific characteristics of implanted patients with PS.

Nonsyndromic patients with an enlarged vestibular aqueduct (NSEVA)

The NSEVA group consisted of 27 children (52% males), after excluding patients with PS, 2 individuals with *PAX3* mutation (Waardenburg syndrome type 1), 3 children with trisomy 21 (Down syndrome), and 1 case of *USH2A* mutation (Usher syndrome type 2a). In 13 of 27 patients, genetic testing indicated monoallelic mutations of the *SLC26A4* gene (*DFNB4*).

All 27 patients at the start of follow-up showed profound HL with an average PTA of 107.9 dB HL (SD 4.4, range: 95–110 dB). There were 16 patients (59%) who had progressive HL, and 8 (29.6%) reported sudden drops in hearing. Progression was significantly associated with a history of sudden drops after minor head trauma.

An additional test was VNG, which demonstrated normal vestibular reactions in 10 children, hyporeflexia in 5 cases, and areflexia in 3. Imaging studies revealed that EVA

was an isolated anatomical finding in 21 patients (78%) and was associated with other anomalies in 6 (22%) individuals, mostly IP-2. The EVA was bilateral in 23 patients (85%). **Figure 2** illustrates a sample MRI scan of a nonsyndromic EVA patient with bilateral enlarged endolymphatic sacs (black arrows)

The mean age at implantation was 6.0 years (SD 4.3, range 0.9–14.6 years). There were 15 children implanted with a Nucleus Freedom implant (Cochlear) and 12 with an N24 implant (Cochlear). There were 6 patients who received simultaneous bilateral implants. No difficulties with electrode fixation in the cochlea were encountered. After cochleostomy, a heart-synchronised oozing of CSF/perilymph appeared in 16 operated ears (49%); active gushing was observed in 5 ears (15%). To prevent further outflow, muscle tissue was packed around the electrode.

After implantation, patients reported transient vertigo (< 24 h), temporary facial nerve paresis (< 4 weeks), soreness when chewing, or aggravation of existing tinnitus. No additional complications were observed. Detailed characteristics of implanted NSEVA patients are listed in **Table 2**.

Nonsyndromic control group

We selected 46 children (61% males) as a control group. Each individual was diagnosed with a profound HL before their CI, with an average PTA score of 107.7 dB HL (SD 4.4, range 95–110 dB). The mean age at implantation was 5.5 years (SD 3.8, range 0.5–15.6 years). The right ear was implanted in 52% of patients; 6 patients underwent bilateral implantation. Two different types of implants were used: Nucleus 22 and Nucleus 24 (Cochlear Corp.), with Freedom or ESPrit 3G speech processors. All patients had

Table 1. Detailed characteristics of patients with Pendred syndrome

No	Sex[a]	Age at HL[b] detection [in months]	Age at first CI[c] [in months]	Age at walking [in months]	Type of HL[d]	HL before CI[e]	Vestibular[f]	CT/MRI result[g]
1	M	6	14	12	cong	prof bil	norm	EVA bil
2	M	4	18	13	cong	prof bil	NA	EVA bil
3	F	8	25	24	cong	prof bil	norm	EVA bil
4	F	10	28	19	cong	prof bil	hypo ×2	EVA bil + IP-2 bil, nFR
5	M	5	12	15	cong	prof bil	norm	EVA bil, nFR
6	M	8	24	13	cong	prof bil	norm	EVA bil
7	F	6	21	14	cong	prof bil	norm	EVA bil, pSS
8	F	7	47	22	prog	prof bil	arefl ×2	EVA bil
9	F	11	50	15	cong	prof bil	norm	EVA bil
10	F	9	49	17	prog	prof bil	NA	EVA bil
11	M	8	59	18	prog	prof bil	NA	EVA bil
12	F	12	56	21	prog	prof bil	hypo ×2	EVA bil + IP-2 bil, pSS
13	M	13	82	12	prog	prof bil	NA	EVA bil
14	M	15	75	13	prog (HT)	prof bil	norm	EVA bil, hM
15	M	9	78	20	prog	prof bil	hypo ×2	EVA bil + IP-2 bil
16	M	7	68	22	prog	prof bil	arefl ×2	EVA bil
17	M	13	135	20	prog (HT)	prof bil	hypo ×2	EVA bil + IP-2 bil, nFR
18	F	10	127	13	prog	prof bil	norm	EVA bil, hM
19	M	7	164	12	prog (HT)	prof bil	NA	EVA bil, nFR
20	F	8	152	16	prog	prof bil	NA	EVA bil
21	F	12	132	20	prog (HT)	prof bil	hypo ×2	EVA bil + IP-2 bil
22	M	14	125	14	prog	prof bil	NA	EVA bil, pSS

Table 1 continued. Detailed characteristics of patients with Pendred syndrome

No	Intraoperative complications[h]	Postoperative complications[i]	CI device[j]	Speech processor	Speech coding strategy	Ear implanted[k]
1	–	–	CI 24	ESPrit 3G	ACE	R
2	perilymph leakage (R,L)	vertigo, tinnitus	CI 22 (I*); CI 22 (II**)	Freedom	SPEAK	R (I); L (II)
3	–	–	CI 22	Freedom	SPEAK	R
4	gusher (R,L)	vertigo, n VII paresis	CI 24 (I); CI 24 (II)	ESPrit 3G	ACE	R (I); L (II)
5	perilymph leakage (L)	n VII paresis	CI 24	ESPrit 3G	ACE	L
6	–	–	CI 24	ESPrit 3G	ACE	R
7	–	–	CI 22	Freedom	SPEAK	L
8	gusher (L)	vertigo, tinnitus	CI 24 (I); CI 24 (II)	ESPrit 3G	ACE	R (I); L (II)
9	–	–	CI 24	ESPrit 3G	ACE	R
10	–	–	CI 22	Freedom	SPEAK	R
11	–	soreness, tinnitus	CI 24 (I); CI 24 (II)	ESPrit 3G	ACE	R (I); L (II)
12	–	soreness	CI 24	ESPrit 3G	ACE	L
13	perilymph leakage (R)	vertigo	CI 22	Freedom	SPEAK	R
14	–	–	CI 24	ESPrit 3G	ACE	L
15	gusher (R,L)	vertigo	CI 22 (I); CI 22 (II)	Freedom	SPEAK	R (I); L (II)
16	perilymph leakage (R)	vertigo, soreness	CI 22	Freedom	SPEAK	R
17	CSF leakage (R)	vertigo	CI 24	ESPrit 3G	ACE	R
18	perilymph leakage (L)	–	CI 24	ESPrit 3G	ACE	L
19	perilymph leakage (R)	n VII paresis	CI 22 (I); CI 22 (II)	Freedom	SPEAK	R (I); L (II)
20	perilymph leakage (R)	soreness	CI 22	Freedom	SPEAK	R
21	gusher (L)	vertigo, tininitus	CI 22	Freedom	SPEAK	L
22	–	–	CI 24 (I); CI 24 (II)	ESPrit 3G	ACE	R (I); L (II)

Note: [a]M, male; F, female; [b]HL, hearing loss; [c]CI, cochlear implantation; [d]cong, congenital; prog, progressive; HT, head trauma; [e]prof, profound; bil, bilateralis; [f]norm, normal, NA, not available; hypo, hyporeflexia; arefl, areflexia; [g]EVA, enlarged vestibular aqueduct; IP-2, incomplete partition type 2; pSS, prodominant sigmoid sinus; nFR, narrow facial recess; hM, hypopneumatization of mastoid; [h]CSF, cerebrospinal fluid; R, right; L, left; [i]n, nerve; [j]CI 22, Cochlear™ Nucleus® 22; CI 24, Cochlear™ Nucleus® 24; [k]R, right ear implanted; L, left ear implanted; *I, first CI implantation; **II, second CI implantation

congenital HL of known etiology in 26% of cases (recessive mutation at a single locus, *GJB2*, or connexin 26).

Imaging studies revealed no substantial inner ear or auditory nerve abnormalities.

Comparison of PS, NSEVA, and NS groups

Comparing the PS, NSEVA, and NS groups, **Table 3** shows the changes in the values of the studied parameters within the observation period (Tlast–T0). For the PTA values, the most significant change from baseline was recorded for PS and NSEVA children compared to NS individuals (means 87.1 and 87.2 dB vs 79.3 dB; $p < 0.001$). However, the increase in both CAP (mean 5 vs 3 and 3; $p < 0.001$) and SIR values (mean 3 vs 2 and 2; $p = 0.002$) was slightly greater in NS children. We did not find significant changes between the studied groups either for MAIS/IT-MAIS or MUSS ($p = 0.884$ and $p = 0.437$, respectively).

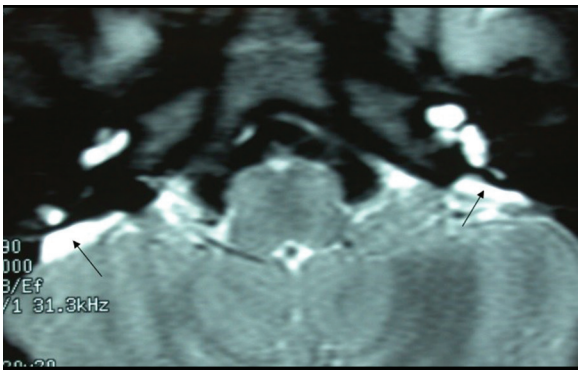

Figure 2. Axial T2-weighted fat-saturated MRI in a 4-year-old girl with nonsyndromic EVA; black arrows point to bilaterally enlarged endolymphatic sacs

Table 2. Detailed characteristics of non-syndromic enlarged vestibular aqueduct (NSEVA) patients

No	Sex[a]	Age at HL[b] detection [in months]	Age at first CI[c] [in months]	Age at walking [in months]	Type of HL[d]	HL before CI[e]	Vestibular[f]	CT/MRI result[g]
1	F	6	19	14	cong	prof bil	norm	EVA bil
2	F	8	11	12	cong	prof bil	norm	EVA bil
3	M	5	12	13	cong	prof bil	NA	EVA uni (L)
4	M	6	22	16	cong	prof bil	NA	EVA bil + IP-2 bil
5	F	8	18	10	cong	prof bil	NA	EVA uni (R)
6	M	5	27	11	cong	prof bil	norm	EVA bil, pSS
7	F	4	26	19	cong	prof bil	hypo ×2	EVA bil
8	M	7	22	13	cong	prof bil	Norm	EVA bil + IP-2 bil
9	M	10	39	15	cong	prof bil	NA	EVA bil
10	F	8	48	14	prog (HT)	prof bil	NA	EVA uni
11	M	12	51	16	cong	prof bil	NA	EVA bil
12	M	13	44	20	cong	prof bil	hypo ×1 (L)	EVA uni (L)
13	F	9	52	14	prog	prof bil	Norm	EVA bil
14	F	7	56	12	prog	prof bil	NA	EVA bil
15	M	16	73	25	prog (HT)	prof bil	arefl ×2	EVA bil + IP-2, pSS
16	F	13	84	19	prog	prof bil	NA	EVA bil, pSS
17	M	10	82	12	prog (HT)	prof bil	norm	EVA bil
18	F	12	71	18	prog (HT)	prof bil	arefl ×2	EVA bil + IP-2 bil
19	F	9	65	15	prog	prof bil	NA	EVA bil + IP-2 bil, nFR, hM
20	M	10	74	12	prog (HT)	prof bil	norm	EVA bil
21	F	22	136	13	prog	prof bil	norm	EVA bil
22	M	25	123	18	prog (HT)	prof bil	hypo ×2	EVA bil + IP-2 bil
23	M	26	138	24	prog	prof bil	arefl ×2	EVA bil
24	M	13	175	12	prog	prof bil	norm	EVA uni (L)
25	F	12	158	18	prog (HT)	prof bil	hypo x2	EVA bil, nFR
26	F	21	153	20	prog (HT)	prof bil	hypo ×2	EVA bil, pSS
27	M	16	172	11	prog	prof bil	norm	EVA bil, hM

Table 2 continued. Detailed characteristics of non-syndromic enlarged vestibular aqueduct (NSEVA) patients

No	Intraoperative complications[h]	Postoperative complications[i]	CI device[j]	Speech processor	Speech coding strategy	Ear implanted[k]
1	perilymph leakage (R)	–	CI 24 (I); CI 24 (II)	ESPrit 3G	ACE	R (I); L (II)
2	gusher (R)	vertigo, tinnitus	CI 22	Freedom	SPEAK	R
3	–	–	CI 24	ESPrit 3G	ACE	L
4	–	–	CI 22	Freedom	SPEAK	L
5	CSF leak (R)	–	CI 24	ESPrit 3G	ACE	R
6	perilymph leakage (R,L)	–	CI 22 (I*); CI 22 (II**)	Freedom	SPEAK	R (I); L(II)
7	perilymph leakage (R)	vertigo	CI 24	ESPrit 3G	ACE	R
8	–	–	CI 22	Freedom	SPEAK	R
9	perilymph leakage (L)	vertigo	CI 24	ESPrit 3G	ACE	L
10	–	–	CI 24 (I); CI 24 (II)	ESPrit 3G	ACE	R (I); L (II)
11	–	soreness, tinnitus	CI 22	Freedom	SPEAK	R
12	perilymph leakage (L)	soreness	CI 24	ESPrit 3G	ACE	L
13	–	–	CI 24	ESPrit 3G	ACE	L
14	perilymph leakage (R)	–	CI 22	Freedom	SPEAK	R
15	gusher (R)	vertigo	CI 22	Freedom	SPEAK	R
16	perilymph leakage (L)	vertigo	CI 22	Freedom	SPEAK	L
17	–	–	CI 24 (I); CI 24 (II)	ESPrit 3G	ACE	L(I); R(II)
18	gusher (L)	vertigo	CI 22	Freedom	SPEAK	L
19	CSF leakage (R)	vertigo, tininitus, n VII paresis	CI 22	Freedom	SPEAK	R
20	–	soreness	CI 24	ESPrit 3G	ACE	R
21	–	soreness	CI 22 (I); CI 22 (II)	Freedom	SPEAK	L (I); R (II)
22	–	tinnitus	CI 22	Freedom	SPEAK	R
23	gusher (R)	vertigo, tininitus	CI 22	Freedom	SPEAK	R
24	–	–	CI 22	Freedom	SPEAK	L
25	perilymph leak (R)	vertigo, n VII paresis	CI 24 (I); CI 24 (II)	ESPrit 3G	ACE	R(I); L(II)
26	perilymph leak (R)	vertigo	CI 22	Freedom	SPEAK	R
27	–	–	CI 22	Freedom	SPEAK	R

Note: [a]M, male; F, female; [b]HL, hearing loss; [c]CI, cochlear implantation; [d]cong, congenital; prog, progressive; HT, head trauma; [e]prof, profound; bil, bilateralis; [f]norm, normal, NA, not available; hypo, hyporeflexia; arefl, areflexia; [g]EVA, enlarged vestibular aqueduct; IP-2, incomplete partition type 2; pSS, prodominant sigmoid sinus; nFR, narrow facial recess; hM, hypopneumatization of mastoid; [h]CSF, cerebrospinal fluid; R, right; L, left; [i]n, nerve; [j]CI 22, Cochlear™ Nucleus® 22; CI 24, Cochlear™ Nucleus® 24; [k]R, right ear implanted; L, left ear implanted; *I, first CI implantation; **II, second CI implantation

A significant difference between the studied parameters was only observed for individual time points (T0–Tlast) between the PS and NSEVA groups and the NS group, but not between PS and NSEVA groups (**Figure 3**). At all time points (T0 – Tlast), measured values of CAP, SIR, MAIS/MAIS-IT, and MUSS in PS and NSEVA children were always significantly higher than in NS children (all $p < 0.001$). However, there were no differences between PS and NSEVA at all measured time points for all investigated parameters. Looking at CAP, both the PS and NSEVA groups established a plateau of their values earlier (from T6 until the end of follow-up) compared with NS children

Table 3. Post-hoc analysis of the change in values of studied parameters (Tlast–T0) across groups of studied children

Value change from baseline (Tlast–T0)				
Parameter	**PS**	**NSEVA**	**NS**	***p***
PTA [dB]	87.1±7.0[a]	87.2±6.3[a]	79.3±8.1[b]	**< 0.001**
CAP	3±1[a]	3±1[a]	5±1[b]	**< 0.001**
SIR	2±1[a]	2±1[a]	3±1[b]	**0.002**
MAIS/IT-MAIS	30±6[a]	29±6[a]	29±4[a]	0.884
MUSS	32±6[a]	32±5[a]	31±5[a]	0.437

Note: [a,b] differences between groups; CAP, categories of auditory performance; IT-MAIS, infant-toddler equivalent of MAIS; MAIS, Meaningful Auditory Integration Scale; MUSS, Meaningful Use of Speech Scale; NS, non-syndromic children; NSEVA, non-syndromic children with enlarged vestibular aqueduct; *p*, probability of obtaining test results (*p*-level below 0.05 set as statistically significant); PS, Pendred syndrome children; PTA, pure tone audiometry; SIR, Speech Intelligibility Rating Scale

(from T8 until the end of follow-up) (**Figure 3a**). In **Figure 3b**, similar differences for SIR values are demonstrated. PS and NSEVA patients from 5 years after CI (T5) had stable values of SIR (plateaus) until Tlast, but NS children established a plateau from 7 years after CI (T7) until the end of follow-up. Similarly, in the PS and NSEVA groups, from 8 years after CI (T8) until the end of follow-up, values of MAIS/IT-MAIS were also comparable (plateaus). Howevert, the NS group did not reach a plateau at any follow-up time (**Figure 3c**). As for MUSS (**Figure 3d**), PS and NSEVA children had comparable values from T8 until Tlast, while NS children established a plateau some 2 years later (from T10).

A multiple regression model was used to pick out significant factors controlling Tlast values of variables among PS, NSEVA, and NS patients. Factors included in the model were patient age, gender, implanted ear (right/left), age of hearing loss diagnosis, duration of hearing loss, age at which a hearing aid was fitted, duration of hearing aid use, and age at cochlear implantation. **Table 4** summarises the factors that were found to have a statistically significant effect on the final outcomes.

Outcomes of PS, NSEVA, and NS children divided by age

All groups of patients experienced significant improvements in speech perception and production. Noticeably, implanted PS and NSEVA patients benefited slightly more from a CI, at least in terms of the mean values of the studied variables and the differences between the groups. **Table 5** summarises and compares values of the parameters among the patients, where they are categorised by age at the last measurement point (Tlast). The PTA scores were significantly higher in the NS group compared to the NSEVA in all age groups. For the CAP parameter, there were no significant differences between the groups, irrespective of age. For the SIR parameter, the final scores differed significantly only in the CAT4 group, where the Tlast score was lower in NS children compared to PS individuals. For the MAIS/IT-MAIS parameter, differences between groups were found in the CAT2–CAT4 age groups, where the Tlast score was significantly higher in the NS group than in the other groups. Furthermore, in CAT2, children with PS achieved significantly lower scores than those with NSEVA. The parameter MUSS was characterised by significant differences between groups in CAT1 and CAT4, where the final Tlast score was significantly lower in the NS group than in the other groups.

After merging the NSEVA and PS groups, we also investigated differences in the values of CAP, SIR, MAIS/IT-MAISS, and MUSS in the sequential measurement points between CAT1 and the others (CAT2–4). At T0, we noticed significantly worse outcomes in the values of all studied parameters in younger children (age < 3 years) compared to others (age > 3 years) ($p < 0.001$). Nevertheless, children in CAT1 had better outcomes at Tlast ($p < 0.05$). As for CAP values, beyond T6 (and until Tlast) we observed a better result for the CAT1 group compared to the CAT2–4 group. Both groups had reached a plateau by T6, but CAT1 showed significantly higher values of CAP after this measurement point ($p < 0.05$) (**Figure 4a**). **Figure 4b** illustrates similar differences in SIR values between age groups. Beyond T7, CAT1 children had better outcomes reflected by this parameter than did older individuals ($p < 0.05$). In both groups, the plateau was established at 5 years after a CI. For MAIS/IT-MAIS, values were comparable between groups from T1 until T5; however, from T6 until the end of follow-up, CAT1 children showed significantly more benefit ($p < 0.05$). Both groups had stable values of MAIS/IT-MAIS from T8 until Tlast (**Figure 4c**). Finally, regarding MUSS values, significant differences between groups were measurable from T6 until Tlast ($p < 0.05$), and the advantage of CAT1 was noticeable. However, both groups reached a plateau beyond T8 (**Figure 4d**).

Impact of "true gushers" and IP-2 malformation on post-CI outcomes

Of all EVA patients, IP-2 malformation was diagnosed in 11 children. Noticeable differences were recorded for PTA, CAP, and SIR. Patients with IP-2 malformation demonstrated worse outcomes than individuals with isolated EVA in PTA ($p < 0.05$), CAP ($p < 0.01$), and SIR ($p < 0.01$) values; however, both subgroups established a plateau at the same measurement point for each value, as shown in **Figure 5**. As for MAIS/IT-MAIS and MUSS, there were no substantial differences in their values between subgroups ($p > 0.05$); however, children with IP-2 established a plateau a year earlier than patients with isolated EVA

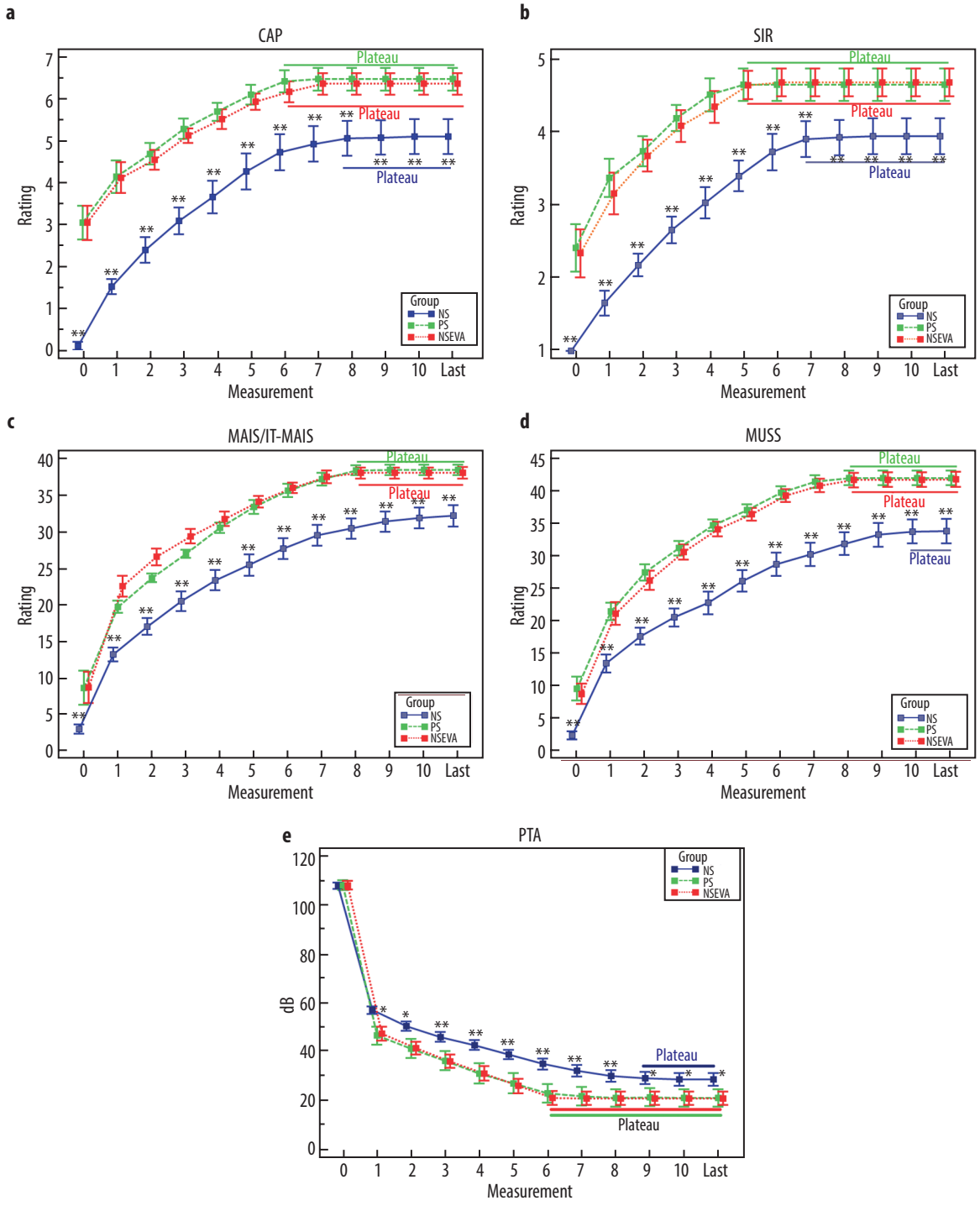

Figure 3. Plots of observed variables before implantation (T0) and for each year after surgery (T1–T10), and at the last available measurement point (TLAST), in three groups of children diagnosed with Pendred syndrome (PS), nonsyndromic enlarged vestibular aqueduct (NSEVA), and a control group of nonsyndromic individuals (NS); (a) SIR variable; (b) CAP variable; (c) MAIS/IT-MAIS variable; (d) MUSS variable; (e) PTA variable; $^{**}p < 0.001$; $^{*}p < 0.05$; error bars, 95% CI

(plateau beyond T7 vs plateau beyond T8). Details are shown in **Figure 5**.

Among all EVA patients, a total of 62 CI implantations were performed. There were 11 ears in which cochleostomy led to a "true gusher", with perilymph leakage lasting more than 1 minute. The occurrence of a gusher did not affect post-implantation outcomes. There were no statistically significant differences between patients with and without gushers in all tested variables (all $p > 0.05$).

Table 4. Factors affecting final post-operative outcomes at Tlast in NSEVA, PS, and NS patients (only statistically significant results are presented)

Variable	Coefficient	Correlation coefficient	*p*
NSEVA			
PTA			
Age at HL	–2.031	0.394	0.364
CAP			
Age	–0.548	–0.506	**0.029**
SIR			
–			
MAIS/IT-MAIS			
–			
MUSS			
Age at CI	–0.05	–0.449	**0.003**
PS			
PTA			
–			
CAP			
Age at HL	–0.156	–0.790	**< 0.001**
SIR			
–			
MAIS/IT-MAIS			
Age at HL	–0.387	–0.732	**< 0.001**
MUSS			
Age	–1.070	–0.516	**0.014**
NS			
PTA			
Age at CI	0.096	0.872	**0.012**
CAP			
Age at CI	–0.022	–0.911	**< 0.001**
Hearing aid usage time	–0.022	–0.899	**< 0.001**
SIR			
Age at CI	–0.018	–0.794	**< 0.001**
Hearing aid usage time	–0.017	–0.780	**< 0.001**
MAIS/IT-MAIS			
Hearing aid usage time	–0.064	–0.961	**< 0.001**
Age	–1.12	–0.954	**0.003**
MUSS			
Hearing aid usage time	–0.075	–0.969	**< 0.001**
Age	–1.96	–0.956	**< 0.001**

Note: CAP, categories of auditory performance; CI, cochlear implantation; HL, hearing loss; IT-MAIS, infant-toddler equivalent of MAIS; MAIS, Meaningful Auditory Integration Scale; MUSS, Meaningful Use of Speech Scale; NS, non-syndromic children; NSEVA, non-syndromic children with enlarged vestibular aqueduct; *p*, probability of obtaining test results (*p*-level below 0.05 set as statistically significant); PS, Pendred syndrome children; PTA, pure tone audiometry; SIR, Speech Intelligibility Rating Scale

Table 5. Final postoperative outcomes (Tlast) in terms of age at first CI (mean ± SE values and significance). ANCOVA analysis including T0 as a covariate

Age group	Group	Parameters (Tlast)				
		PTA	CAP	SIR	MAIS/IT-MAIS	MUSS
0–3 years (CAT1)	**NSEVA** (*n* = 8)	13.8±4.3	6.8±0	4.9±0	40.0±2	43.3±2
	PS (*n* = 7)	14.6±4.5	6.7±0	4.9±0	34.0±1	43.4±1
	NS (*n* = 15)	19.3±4.6	6.7±0	4.5±1	36.0±1	40.3±1
	p	0.002	0.988	0.263	0.305	**< 0.001**
	Differences	**NS vs NSEVA**	–	–	–	**NS vs PS NS vs NSEVA**
4–5 years (CAT2)	**NSEVA** (*n* = 5)	20.7±4.0	6.6±1	4.2±1	32.0±1	40.2±1
	PS (*n* = 6)	21.7±6.3	6.7±1	4.1±1	23.0±2	39.5±2
	NS (*n* = 11)	27.5±3.7	4.8±1	4.1±1	41.0±1	37.1±3
	p	**0.009**	0.324	0.900	**< 0.001**	0.899
	Differences	**NS vs NSEVA**	–	–	**NS vs NSEVA NS vs PS PS vs NSEVA**	–
6–7 years (CAT3)	**NSEVA** (*n* = 6)	23.1±5.8	6.0±1	4.1±1	21.6±2	40.7±3
	PS (*n* = 4)	23.6±6.2	5.2±1	4.3±1	23.3±2	40.4±3
	NS (*n* = 10)	32.1±4.8	5.2±1	4.1±1	41.3±2	35.7±2
	p	**0.030**	0.969	0.977	**< 0.001**	0.830
	Differences	**NS vs NSEVA**	–	–	**PS vs NS NSEVA vs NS**	–
> 8 years (CAT4)	**NSEVA** (*n* = 7)	26.4±5.2	4.3±1	4.1±1	24.6±2	40.0±4
	PS (*n* = 6)	26.7±9.3	4.3±1	4.3±1	22.6±2	40.0±3
	NS (*n* = 10)	39.0±5.2	58±1	3.4±1	39.9±2	24.7±2
	p	**0.001**	0.793	**0.012**	**< 0.001**	**< 0.001**
	Differences	**NS vs NSEVA**	–	**PS vs NS**	**PS vs NS NSEVA vs NS**	**PS vs NS NSEVA vs NS**

Note: CAP, categories of auditory performance; CAT, age category; CI, cochlear implantation; HL, hearing loss; IT-MAIS, infant-toddler equivalent of MAIS; MAIS, Meaningful Auditory Integration Scale; MUSS, Meaningful Use of Speech Scale; NS, non-syndromic children; NSEVA, non-syndromic children with enlarged vestibular aqueduct; *p*, probability of obtaining test results ($p < 0.05$ set as statistically significant); PS, Pendred syndrome children; PTA, pure tone audiometry; SIR, Speech Intelligibility Rating Scale

Discussion

Cochlear implantation is a safe and effective treatment for severe-to-profound HL in children with EVA for whom conventional amplification aids are inadequate. Post-implantation outcomes proved to be highly successful overall, with a low rate of complications despite the abnormal inner ear anatomy [35–39]. This study confirmed the efficacy of cochlear implants for dealing with HL in patients with EVA. However, it is difficult to predict the benefits and limitations of CIs due to the impact of various factors such as age at CI, residual hearing, inner ear malformation, cochlear nerve deficiency, parent–child interactions, and socioeconomic status [40–43]. In our study, the patient's age at implantation, age at HL detection, duration of HA use, and the presence of additional IEMs significantly impacted postoperative outcomes (all $p < 0.05$). Other factors, such as gender, side of implantation, and the presence of a gusher after performing a cochleostomy, had no significant effect on post-implantation results (all $p > 0.05$). Of the factors mentioned above, the age of implantation appeared to be the most influential in determining postoperative outcomes, a result which has also been confirmed in extensive studies [6,7,44,45].

In this study, NSEVA and PS children implanted before 3 years of age performed better than older individuals. In general, the final result was better if the implantation was performed earlier. Such a result probably depends on brain plasticity during early childhood. Several studies have demonstrated the presence of a sensitive period, ending around 3–4 years of age, in which the central auditory pathways exhibit the greatest neural plasticity [46,47]. Kileny et al. [44] observed that children implanted under

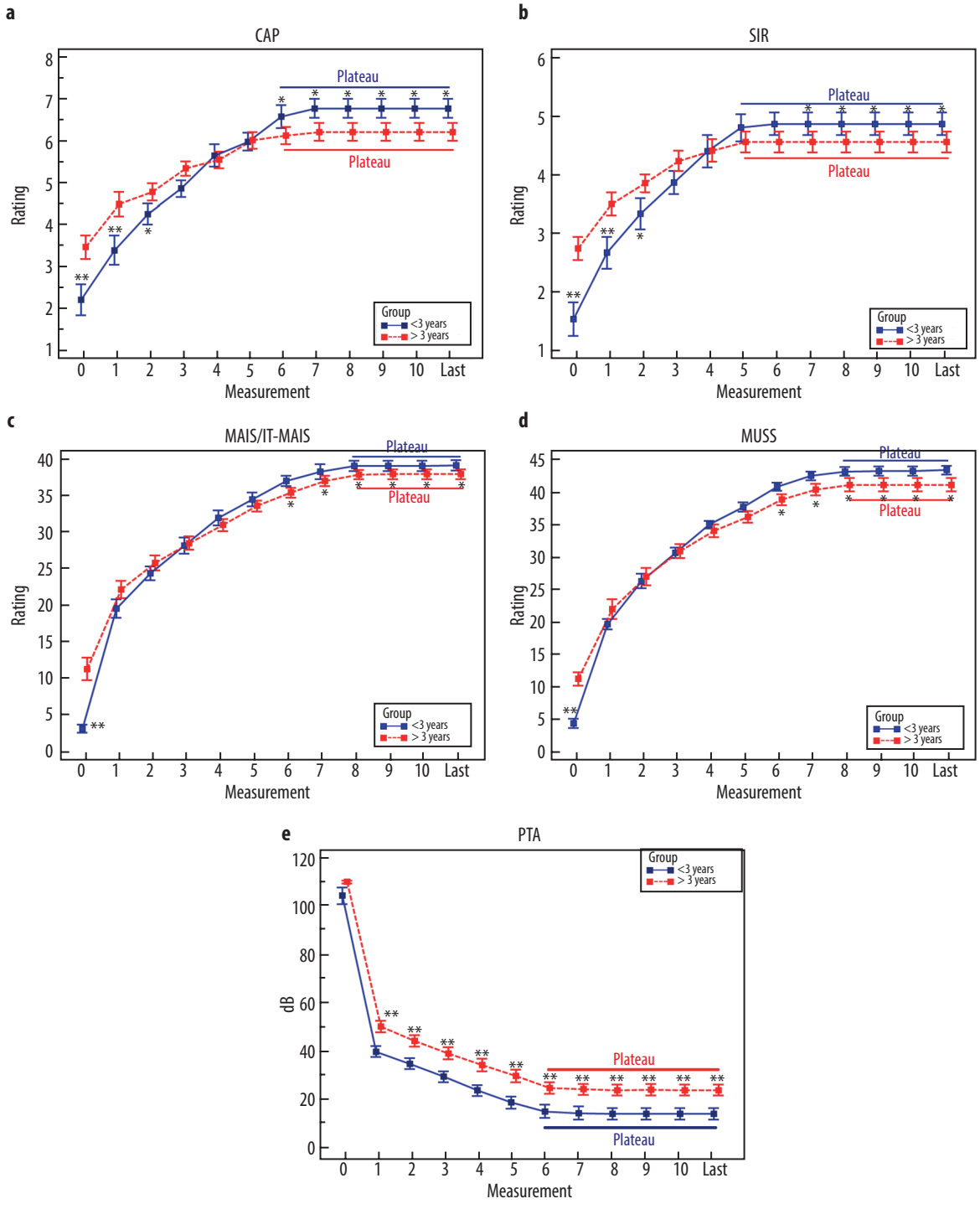

Figure 4. As for **Figure 3** but divided into age categories based on their age at the first cochlear implant (CAT1, < 3 years vs CAT2–4, > 3 years)

3 years of age outperformed patients who received implants later in life. Likewise, Govaerts et al. [9] reported excellent audiologic outcomes in children implanted prior to 2 years of age, with an increased likelihood of age-appropriate CAP scores in the initial postoperative period. Geers et al. [48] also defined 2 years of age as the cutoff for optimal CI performance and found an association between children implanted after 2 years of age and poorer CAP outcomes. Considering the abovementioned reports, we have established the age of 3 as the borderline between early and late implantation.

The progressive nature of HL in the EVA population permits fundamental communication skills to continue to develop if residual auditory function is preserved [49]. This explains why older EVA children achieved higher

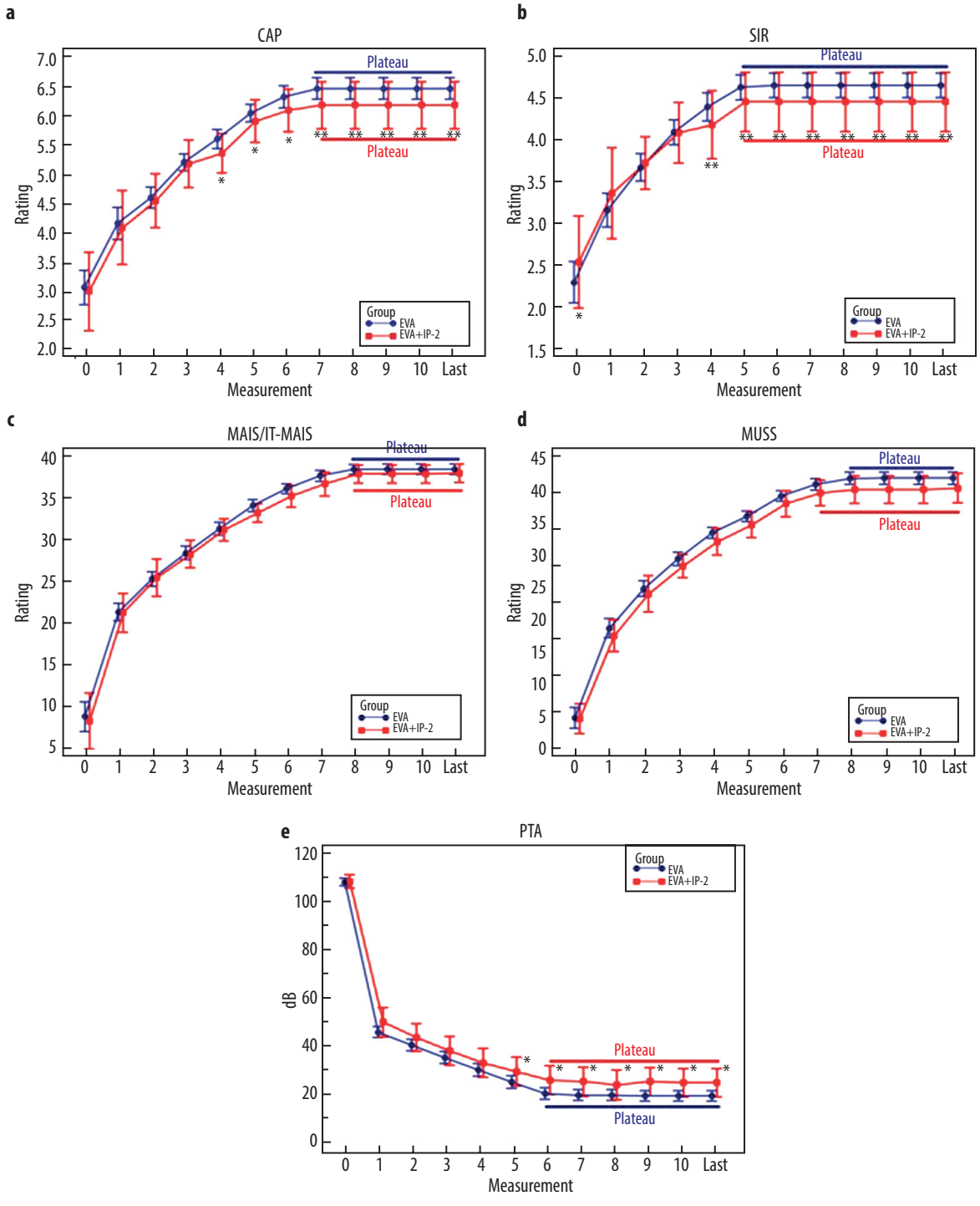

Figure 5. As for **Figure 3**, but for the EVA group only and categorised into those with and without IP-2

scores before implantation than younger EVA individuals. Nonetheless, it is intriguing to note that, over the entire observation period, EVA children implanted at a younger age outperformed older EVA patients in terms of auditory and speech skills after about 5–6 years of follow-up. This is further evidence that early implantation benefits EVA patients. In this study, the benefits of a CI were comparable for both NSEVA and PS patients, similar to the study by van Nierop et al. [49], where patients with NSEVA and PS were considered comparable in terms of preoperative counselling for their expected auditory performance. Studies by McKay [50] and Dettman et al. [51] have also demonstrated improvement in outcomes when a CI is received at an earlier age (with worse audiological, speech, and language outcomes as duration of deafness increases). Additionally, we observed that EVA children performed better and faster than NS individuals, both in the younger and older age groups. Similarly, in the study by

Demir et al. [52], children with EVA achieved higher final CAP and SIR scores than the control group. In contrast, Colvin et al. [53] noticed that patients with Pendred syndrome had worse outcomes than nonsyndromic patients.

However, in those EVA patients who exhibit progressive HL but have a tendency for thresholds to fluctuate, determining the optimal timing of implantation is challenging. There is a theory that patients with inner ear malformations, especially with EVA, may meet the criteria for implantation later (compared to controls with congenital HL) due to the progression of HL [54]. Due to the instability of patients with fluctuating HL, some parents hesitate to proceed with surgery when spontaneous improvement is possible. According to Sweetow et al. [55], researchers have explored the potentially "tragic failure" of losing residual hearing due to premature implantation in a child who may spontaneously regain sufficient hearing to benefit from a hearing aid. However, they state that delays in implantation might be due to emotional and social factors, and concluded that hybrid implants might be the best option for fluctuating HL.

On the other hand, Gratacap et al. [56] and Mikkelsen et al. [57] concluded that cochlear implantation should not be delayed in patients with fluctuating HL because of the impact on the development of speech and language. Indeed, it has been argued that fluctuating HL is an indication to avoid the delay of CI [58]. Ko et al. [59] recommend that patients, especially if their hearing function has not recovered after 3 months of HA use, should not wait until their hearing threshold exceeds 90 dB HL to benefit from a CI. In addition, they cautioned against using snapshot assessments of auditory performance, such as the CAP and the phonetically balanced word test, in patients with unstable or fluctuating hearing loss, preferring speech intelligibility and perception tools instead. Therefore, our study evaluated the average CAP scores over time and included other speech intelligibility scales and parental questionnaires.

Parent-reported outcomes provide an understanding of the development of children's auditory behaviors and speech production and allow an assessment of how well clinical tests, such as speech perception tests, correlate with a child's performance in their natural environment. Accordingly, we used the well-validated MAIS, IT-MAIS, and MUSS scales for such assessment. In this study, there were no statistically significant post-implantation differences between NSEVA and PS patients, while differences emerged between EVA patients and the control group. Such insights are similar to those of many other studies [60,61].

As is well known, children with inner ear malformations may experience speech or hearing impairments after receiving a CI. It is estimated that 20% of children with congenital SNHL may have inner ear malformations, with EVA being the most common [60–62]. Several studies have found that after a CI, patients with EVA have comparable hearing ability and speech recognition outcomes to patients with normal inner ear anatomy [38,39]. Buchmann et al. [62] noted that children with a constellation of IP, EVA, and a dilated vestibule (i.e., Mondini's malformation) performed very well on speech perception tests, with at least 10 (63%) of 16 patients achieving some degree of open-set speech recognition. Individuals with isolated EVA likewise perform well, with 8 of 9 (89%) achieving open-set recognition. These results corroborate our study's observations that audiological results were not affected by the presence of an enlarged vestibular aqueduct, in contrast to IP-2. In our study, the results of children with EVA are even higher than those with normal inner ear anatomy. The phenomenon quoted above may arise because hearing loss in EVA patients is closely related to inner ear dysfunction. Wu et al. [63] reported that the genetic expression of Pendred syndrome is limited to the inner ear, sparing the pathways from the auditory nerves to the central auditory system. This observation may explain why children with PS may achieve better post-implantation outcomes than those with HL of unknown etiology, in which there is a higher risk of spiral ganglion neuron degeneration (perhaps associated with slower progression after implantation). Comparing patients with an additional ear anomaly in the form of IP-2 to those with only EVA, we found that these children achieved worse final scores on the CAP and MAIS/IT-MAIS scales, as well as in PTA. In contrast, no differences were observed on the SIR and MUSS scales. However, the patient population is small, so conclusions should be cautiously drawn.

Another aspect considered in our study was the use of imaging studies to plan surgery and avoid potential complications. Several studies have illustrated the importance of a thorough preoperative radiological examination to classify cochlear and/or vestibular anomalies before surgery [64,65]. Abnormal HRCT or MRI scans may predict compromised cochlear patency, thus anticipating difficulties with device insertion [7,23]. These scans may indicate potential for intraoperative CSF leakage [66], but not always [62]. In addition, imaging may determine the direction of electrode insertion to avoid osseous defects [67], prevent damage [68], and guide the decision to use a straight, curved, or double array electrode.

Children with cochlear anomalies may be at higher risk for cerebrospinal fluid/perilymph leakage due to patent areas of the otic capsule. A thin or absent cribriform region may exist between the modiolus and the internal auditory canal. During cochleostomy and before inserting the electrode array, there may be a profuse flow or 'gush' of cerebrospinal fluid [66,67]. Several recent reviews indicate that, in cases of cochlear malformation, the incidence of gushers during CI ranges from 7 to 50% [1,43,62,68–70]. In our study, among 62 implantations performed on EVA patients, CSF/perilymph leakage was observed in 50% of cases, the upper figure estimated in the literature. In a study by Pakdaman et al. [70], the incidence of gushers during a CI depends on the type of inner ear malformation. The authors found the incidence of CSF leakage to be 18% in patients with IP-2 malformation and 40% in isolated EVA. Comparing the previous results to our observations, we noted the incidence of CSF/perilymph leakage in 32% of ears with isolated EVA and in 41% of ears with EVA+IP-2. Looking at the incidence of "true gushers", we also noted an advantage in ears with EVA+IP-2 compared to ears with isolated EVA (18% vs 4%). Nevertheless, the prevalence of gushers may be significantly overestimated. If we adopt the criterion of Papsin [43], who argued that only pulsatile leakage of CSF for over 1 minute should be classified

as a "true gusher", its incidence may in fact be much lower. In our study, true gushers were observed in 18% of 62 implantations in EVA children, which was lower than expected, considering that all patients had EVA or other inner ear malformation. Administration of a mannitol drip to certain EVA patients during the CI procedure may explain the low percentage of patients experiencing a true gusher. Other strategies used to reduce the risk of gusher/oozing include intraoperative lowering of pCO_2 and administering postoperative oral acetazolamide, head elevation, lumbar drain, or reverse Trendelenburg position [71]. The perilymph release observed in our study was limited and brief, requiring no further steps besides tight packing with small pieces of temporal muscle.

A possible concomitant risk for children with cochlear or vestibular anomalies is the incomplete insertion of the electrode array, leading to fewer channels available for programming. The number of active electrodes in place correlates positively with children's speech perception, production, spoken language, and overall language outcomes [72]. In our study, all electrodes were fully inserted into the scala tympani, both in patients with EVA occurring in isolation and in those with EVA and IP-2 (historically called Mondini malformation). The results are comparable to the findings of many authors, who have commonly encountered difficulties with cochlear electrode insertion with other types of malformations, such as common cavity deformity (CCD) [23] or cochlear hypoplasia [69]. The complications that occurred intra- or post-operatively did not adversely affect post-implantation outcomes.

This research provides evidence that EVA patients are excellent candidates for implantation. However, we are aware of several limitations of this research. First, the study is a retrospective review with a relatively small patient population. This is especially noticeable when evaluating the impact of a gusher or the presence of an IP-2 malformation on post-implantation outcome. Other limitations include the subjective testing, the absence of complete genetic testing, and the potential impact of unknown hearing etiology on post-implantation outcomes. We believe that cochlear implant centers should collaborate internationally and use common research tools for measuring prospective follow-up.

Conclusions

The present study has demonstrated that all patients with EVA received improved auditory and speech outcomes after cochlear implantation. The benefits of a CI were greater the earlier the implantation was performed, which was true of all groups analysed. On this basis, patients with EVA, who commonly exhibit progressive or fluctuating HL, should not be deferred from deciding in favour of a CI. However, the presence of EVA had a significant impact on a higher incidence of gushers/oozing, and these require additional interventions to stop further leakage. In practice, the incidence of gushers/oozing did not affect speech and auditory outcomes, the incidence of intra- or post-operative complications, or difficulties with implant electrode fixation. The diagnosis of Pendred syndrome had no impact on post-implantation outcomes, but it is essential to monitor thyroid function and determine the most appropriate treatment.

Among congenital anomalies of the inner ear, in addition to the well known EVA, the second most common anomaly assessed by imaging studies was IP-2 malformation. We found that this defect did not affect the course of CI implantation but did significantly affect post-implantation outcomes. Patients with additionally diagnosed IP-2 achieved poorer results after a CI.

Looking to the future, research should consider appropriate preoperative planning, selection of appropriate electrodes to control gushers, standardised tests for outcome measures, and careful consideration of factors that may affect outcomes.

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