Outcomes of Cochlear Implantation in Patients with Pendred syndrome: A Systematic Review and Narrative Synthesis

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Establish outcomes following cochlear implantation (CI) in patients with Pendred syndrome. Systematic review and narrative synthesis. Databases searched: Medline, Pubmed, Embase, Web of Science, Cochrane Collection and ClinicalTrials.gov. No limits placed on language or year of publication. Review conducted in accordance with the PRISMA statement. Searches identified 251 abstracts and 242 full texts. Of these, 22 studies met inclusion criteria reporting outcomes in 231 patients with at least 234 implants. Hearing outcomes were generally good with patients experiencing useful functional improvement. A total of 46 minor complications were reported in 78 cases. The methodological quality of included studies was modest, predominantly consisting of case reports and non-controlled case series with small numbers of patients. All studies were OCEBM grade III-IV. Hearing outcomes following CI in Pendred syndrome are generally good with useful functional improvement. However, outcomes reported in published studies lack long term follow up.

KEYWORDS: Pendred syndrome, cochlear implants, systematic review

INTRODUCTION

Background and Epidemiology
Pendred syndrome is an autosomal recessive condition resulting in profound to severe sensorineural hearing loss, defective iodine organification, and goiter, typically presenting without hypothyroidism [1]. It was first described by Dr. Vaughan Pendred in an article in “The Lancet” as an association between deaf-mutism and thyroid goiter in 1896 [2]. A century later, in 1996, the genetic basis of Pendred syndrome was elucidated with the defect localized to SLC26A4/PDS located on chromosome 7q21-34 [3,4]. The clinical manifestations present as a result of biallelic mutations in the SLC26A4 gene on chromosome 7, which encodes pendrin, a multifunctional anion exchanger expressed in the inner ear, thyroid, and kidneys. In the inner ear, it plays a vital role in maintaining the endolymph composition and endocochlear potential by functioning as a chloride/bicarbonate exchanger [5]. However, some controversy exists as to whether it may also function as a sulfate transporter owing to a similar structure to other sulfate transporters [6].

Pendred syndrome is the most common cause of syndromic hearing loss and congenital hearing loss, accounting for 7.5%-15% of cases [7]. The incidence is reported as 7.5 to 10 in 100,000 [8].

The predominant inner-ear malformation in Pendred syndrome is an enlargement of the endolymphatic system, which can be visualized as an enlarged vestibular aqueduct (EVA) on magnetic resonance imaging (MRI) or computed tomography (CT) [9]. Although this is not exclusive to Pendred syndrome, subjects may also have incomplete partition type II (Mondini dysplasia), a deficient interscalar septum in the distal coils of the cochlea [10]. These malformations are common, with abnormalities including EVA with or
without enlarged endolymphatic sac (EES) and/or Mondini malformation identified in 86% of cases [7]. The true rate may be even higher than this, with Mondini deformity present in 20% and EVA present in 82.5% of cases on CT and in 100% of cases on MRI [10]. Hearing loss is typically prelingual and bilateral and ranges from severe to profound, with a fluctuating pattern of progression [11,12].

Diagnosis
There are a number of possible routes for diagnosis. Historically, this was a clinical diagnosis of hearing loss with thyroid goiter. Hearing loss is typically progressive but may be sudden after a head injury in the presence of EVA. This was then supplemented by the perchlorate discharge test and, more recently, by genetic testing. A positive perchlorate test distinguishes Pendred syndrome from other forms of EVA. In terms of genetic testing, the presence of a biallelic (pertaining to both alleles of a single gene) SLC26A4 mutation is diagnostic for Pendred syndrome [13].

Risk during Cochlear Implantation
There are no specific risks associated with cochlear implantation in patients with Pendred syndrome, although EVA has been suggested as a possible risk for ongoing cerebrospinal fluid (CSF) leak [14]. Hearing outcomes are typically thought to be good.

Objectives
Patients with hereditary forms of deafness have been noted to perform better than adults without a hereditary cause [15]. In this review, we aimed to look at cochlear implant (CI) outcomes from this syndrome, complications, and perioperative considerations.

Population: Children or adults with Pendred syndrome.
Intervention: Cochlear implantation.
Comparison: Comparison within the group depending on the type of anatomical variant present, e.g., EVA versus Mondini dysplasia versus non-reported.
Outcomes: Pre- versus postimplantation audiometric outcomes (where preimplantation outcomes were not available, only postimplantation audiometric outcomes were included). Complications associated with perioperative period in patients receiving cochlear implantation.

MATERIALS AND METHODS
The study protocol was registered in the PROSPERO prospective database of systematic reviews (193650).

Study Inclusion Criteria
There are clinical studies of cochlear implantation in patients with Pendred syndrome with hearing outcomes reported at a minimum of 3 months postimplantation. Diagnosis of Pendred syndrome may be clinical or genetic and of any subtype. Studies of any experimental or observational design in humans were included. Animal and human studies without a report of postoperative audiometric outcomes or where the abstract or full text was unavailable were excluded.

Search Strategy
In total, 2 reviewers (KB/AL) independently performed the searches and screened the abstracts. The following databases were searched: MEDLINE, PubMed, EMBASE, Web of Science, Cochrane Collection, and ClinicalTrials.gov (via Cochrane).

The search terms used were as follows:
1) “Cochlear Implants”
2) “Cochlear Implantation”
3) Cochlear Implant* (title)
4) 1 OR 2 OR 3
5) “Pendred syndrome”
6) Pendred* (title)
7) SLC26A4*
8) PDS*
9) DFNB4
10) 5 OR 6 OR 7 OR 8 OR 9
11) 4 and 10

No limit was placed on language or year of publication.

Selection of Studies
Searches were performed by an Information Specialist Librarian (Matthew Stone). The 2 reviewers (KB/AL) independently screened all the records by title and abstract identified from the database searches. Studies describing cochlear implantation in patients with Pendred syndrome were assessed against the inclusion and exclusion criteria, with any disagreement resolved by discussion with a third reviewer (CM). Studies without accessible abstract or full text after the title/abstract screening were followed up by attempting to contact the respective study authors. If they remained unavailable, the study was excluded. Studies were excluded if they did not report postintervention audiometric outcomes at a minimum of 3 months post-procedure. Studies presenting overlapping populations were limited to the largest study sharing data if it is not possible to disambiguate them. Potentially relevant studies identified from the initial searches and abstract screening then underwent full-text screening by the 2 independent reviewers before data extraction. Conflicts on the selection were resolved by discussion between the reviewers.

Data Extraction
Data were extracted by the first reviewer (KB) and then checked by a second reviewer (AL). Extracted data were arranged in a spreadsheet (Excel, Microsoft Corp., Redmond, WA, USA).

Risk of Biased Quality Scoring
The 2 reviewers independently assessed the risk of bias using the Brazzelli risk of bias tool for nonrandomized studies [16]. Studies were also graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) grading system [17]. Discrepancies between the reviewers were resolved by discussion.
RESULTS

Searches were initially performed on May 20, 2020 and rechecked on June 9, 2020. A flowsheet detailing the study selection according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [18] is included in Figure 1.

Description of Studies

A total of 22 studies met the inclusion criteria with a total of 231 patients and at least 234 implants. There were 9 case series, 2 case-control studies, and 5 cohort studies, which included 2–42 patients, plus 6 single-case studies. All studies were published between 2001 and 2019. A total of 15 studies included pediatric patients only, 5 studies included both adults and children, and 2 were case reports of adults. The age at time of cochlear implantation ranged from 10 months to 65 years; however, reporting of age varied even within the studies. A total of 18 studies reported on the type of implant used [12,19-35]. Moreover, 13 studies reported a genetic analysis for included patients, reporting a range of mutations in the SLC26A4/PDS gene [12,21,23,24,26-28,30,31,34,36-38]. Preoperative radiological assessment of anatomy was reported in 17 studies, with reported findings as 148 EVA (14 with EES) and 36 Mondini/cochlear dysplasia cases. Study characteristics are summarized in Table 1.

Table 1. Study characteristics

| Study                  | Year | Country    | Number of patients | Population     | Study type                     | OCEBM* Grade |
|------------------------|------|------------|--------------------|----------------|--------------------------------|---------------|
| Broomfield et al.      | 2013 | UK         | 7                  | Children       | Retrospective case series      | IV            |
| Chiong et al.          | 2018 | Philippines | 4                  | Adults and children | Retrospective case series   | IV            |
| De Wolf et al.         | 2010 | Netherlands | 2                  | Children       | Retrospective case series      | IV            |
| Demir et al.           | 2019 | Turkey     | 18                 | Adults and children | Retrospective case-control    | IV            |
| Fahy et al.            | 2001 | UK         | 4                  | Children       | Retrospective case series      | IV            |
| Gratacap et al.        | 2015 | France     | 14                 | Children       | Retrospective case series      | IV            |
| Ko et al.              | 2013 | Taiwan     | 42                 | Adults and children | Retrospective case-control    | IV            |
| Kontorinis et al.      | 2011 | Germany    | 5                  | Adults and children | Retrospective case series     | IV            |
| Kuthubutheen et al.    | 2012 | Australia  | 1                  | Child          | Prospective case report        | IV            |
| Loundon et al.         | 2005 | France     | 11                 | Children       | Retrospective cohort study     | III           |
| Mikkelsen et al.       | 2019 | Denmark    | 1                  | Child          | Retrospective case report      | IV            |
| Park et al.            | 2017 | Korea      | 9                  | Children       | Retrospective case series      | IV            |
| Roh et al.             | 2017 | Korea      | 8                  | Children       | Retrospective case series      | IV            |
| Steinbach et al.       | 2006 | Germany    | 1                  | Adult          | Retrospective case report      | IV            |
| Sweetow et al.         | 2005 | USA        | 1                  | Child          | Retrospective case report      | IV            |
| Vaisbuch et al.        | 2019 | USA        | 1                  | Adult          | Retrospective case report      | IV            |
| van Nierop et al.      | 2016 | Netherlands | 28                 | Adults and children | Retrospective cohort study   | III           |
| Wu et al.              | 2008 | Taiwan     | 18                 | Children       | Prospective cohort study       | III           |
| Wu et al.              | 2011 | Taiwan     | 22                 | Children       | Prospective cohort study       | III           |
| Wu et al.              | 2015 | Taiwan     | 23                 | Children       | Prospective cohort study       | III           |
| Yamazaki et al.        | 2014 | Japan      | 1                  | Child          | Retrospective case report      | IV            |
| Yan et al.             | 2013 | China      | 10                 | Children       | Retrospective case series      | IV            |

*Oxford Centre for Evidence-Based Medicine
| Study                  | Preoperative data                                                                 | Postoperative data                                                                 | Overall benefit (subjective assessment)           | Follow-up |
|-----------------------|----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------|-----------|
| Broomfield et al.     | Not reported                                                                      | Speech perception scores: BKB scores recorded in n=3 (70%, 79%, and 94%) SRS: grade 6 (3), grade 5 (2), grade 2 (1), nonuser (1). Mode of communication: speech (3), speech + sign (3), sign (1). 6/7 attended mainstream school (4 of which had hearing impairment unit), 1 attended school for deaf. | Good outcomes in PS. Cognition may influence success of CI | 68 months |
| Chiong et al.         | Pure-tone audiometry: PTA threshold (median) for 4 patients: patient 1: 110, patient 2: 120, patient 3: 107.5, patient 4: 120 | Pure-tone audiometry: PTA threshold (median) for 4 patients: patient 1: 30, Patient 2: 42.5, Patient 3: 37.5, patient 4: NA. Speech perception scores: Overall PEACH score: Patient 1: 0.86, Patient: 20.62, Patients 3 and 4: NA. | SLC26A4 c.706C>G (p.Leu236Val) variant does not adversely affect post-CI hearing outcomes | 6.5 years |
| De Wolf et al.        | Pure-tone audiometry: Sibling 1: (age 4.2 years): 63 dB (right), 77 dB (left), age 5.5 years: >110 dB (right), 90 dB (left) 75% at 95 dB with hearing aid in left ear. Sibling 2: Fletcher index 90 dB (right),55dB (left), with BL hearing aids: Speech perception scores: Phoneme score 75% at 70 dB, left only: 9% speech recognition, Right 54%. | Pure-tone audiometry: Sibling 1: Fletcher index greatly improved, stabilizing at 25 dB at 14 months postimplantation. Speech perception scores: In sibling 1, word score and speech on monosyllable identification test was 75% at 2 months and 100% at 6 months. Phoneme scores were 91% at 14 months. For sibling 2, the phoneme score was 89% at 2 months (compared with 75% with bilateral hearing aids preimplantation) | CI is successful despite cochlear hypoplasia | 2–24 months |
| Demir et al.          | Pure-tone audiometry: PTA in LVAS group: mean 109.83 (±17.29), median 111.5 (78–130). PTA in control: mean 110.83 (±18.54), median 101(75–130). Speech perception scores: SIR in LVAS group: mean 2.56 (±1.58), median 2 (1–5). SIR in control: mean 1.72 (±1.23), median 1 (0–5). CAP in LVAS group: mean 3.17 (±2.5), median 3 (0–7). CAP in control: mean 1.22 (±1.66), median 0 (0–5). WDS in LVAS group: mean 10 (±13.94), median 0 (0–40). WDS in control: mean 2 (±8.49), median 0 (0–36). | Pure-tone audiometry: PTA in LVAS group: mean 32 (±2.44), median 30 (20–60). PTA in control: mean 29.94 (±1.73), median 30 (18–50). Speech perception scores: SIR in LVAS group: mean 4 (±1.57), median 5 (1–5). SIR in control: mean 4.5 (±1.58), median 5 (1–9). CAP in LVAS group: mean 6.11 (±1.81), median 7 (2–9). CAP in control: mean 5.94 (±1.63), median 7 (1–7). WDS in LVAS group: mean 54.89 (±35.96), median 66 (0–100). WDS in control: mean 60.44 (±30.4), median 70 (0–96). | Patients with LVAS benefit from CI | x |
| Fahy et al.           | Pure-tone audiometry: Aided PTA thresholds dB (kHz): Patient 1: 30 (0.5), 30 (1), 55 (2), 75 (4), Patient 2: 40 (0.5), 40 (1), 45 (2), 53 (4), Patient 3: 35 (0.5), 30 (1), 45 (2), 50 (4), Patient 4: 49 (0.5), 38 (1), 55 (2), 64 (4). Speech perception scores: LiP: Patient 1: 17, Patient 2: 37, Patient 3: 10, Patient 4: 22. CAP scores: Patient 1: 4 Patient 2: 5, Patient 3: 3, Patient 4: 5. | Pure-tone audiometry: Aided PTA thresholds dB (kHz): Patient 1: 34 (0.5), 32 (1), 31 (2), 32 (4), Patient 2: 38 (0.5), 35 (1), 30 (2), 35 (4), Patient 3: 40 (0.5), 26 (1), 36 (2), 34 (4), Patient 4: 40 (0.5), 40 (1), 35 (2), 30 (4). Speech perception scores: Score at 12 months post-op. LiP: Patient 1: 42, Patient 2: 42, Patient 3: 42, Patient 4: 42. CAP scores: Patient 1: 5, Patient 2: 6, Patient 3: 5, Patient 4: 5. | Good audiological improvement in all children, especially at higher frequency ranges | 12 months |
| Gratacap et al.       | Pure-tone audiometry: Preoperative mean: nonaided PTA threshold: mean 101, median 100 (87–117), aided PTA threshold: mean 67, median 63 (42–105), | Speech perception scores: OSW at 12 months: mean 74, median 82 (10–100), OSW at 24 months: mean 81, median 90 (40–100) | Good performance with CI (no subgroup analysis by etiology) | 24 months |
### Table 2. Summary of audiological outcomes

| Study            | Preoperative data                                                                 | Postoperative data                                                                 | Overall benefit (subjective assessment) | Follow-up |
|------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------|-----------|
| Ko et al.        | Speech perception scores: SIR in early LVAS: mean 1.9 (±1.1), median 1.5 (1–4). SIR in late LVAS: mean 3.7 (±1.3), median 4 (1–5). CAP in early LVAS: mean 2.4 (±2.0), median 2 (0–6). CAP in late LVAS: mean 4.0 (±2.0), median 4 (1–7). Non-LVAS: SIR 1.7 (±1.1), median 1 (1–5), CAP 2.1 (±1.6), median 1 (1–6) | Speech perception scores: SIR in early LVAS at 12 months: mean 3.4 (±1.1), median 3 (2–5). SIR in early LVAS at most recent test (mean duration of CI use 7.3 (±3.5); mean 4.5 (±0.9), median 5 (2–5). SIR in late LVAS at 12 months: mean 4.2 (±1.1), median 5 (1–5). SIR in late LVAS at most recent test (mean duration of CI use 4.6 (±3.3); mean 4.3 (±1.2), median 5 (1–5). CAP in early LVAS at 12 months: mean 5.0 (±1.1), median 5 (3–7). CAP in early LVAS at most recent test: mean 6.2 (±0.9), median 6 (4–7). CAP in late LVAS at 12 months: mean 5.5 (±1.4), median 6 (2–7). SIR in late LVAS at most recent test: mean 6.0 (±1.2), median 6 (3–7). Early group Mean speech perception tests at 12 months: 48.1±26.1 (tone), 76.3±29.1 (sentence), 82.9±7.6 (PB word). At most recent test: 67.2±32.5 (tone), 92.6±16.6 (sentence), 86.7±13.3 (PB word). Late group Mean speech perception tests at 12 months: 67.3±19.1 (tone), 80.6±25.4 (sentence), 80.3±15.1 (PB word). At most recent test: 76.8±15.2 (tone), 84.8±25.4 (sentence), 81.7±13.3 (PB word). | High levels of speech performance are reached after 5 years of implant use in patients with LVAS | 5.8 years |
| Kontorinis et al. | Pure-tone audiometry: Patients 1 and 2: no data, patient 3: PTA 100dB (right), 90dB (left), Patient 4: PTA 80dB (right), 70dB (left), AEP 80 dB (left), 80 dB (right), Patient 5: PTA 80 dB(left), promontory test positive (left) | Patient 1 (with 1 CI): FDA-test: Good reactions to all sounds at first fitting, 3 months, 12 months, satisfactory results at 24 months. Speech recognition and development at 12 months, further development at 24 months. Patient 1 (with 2 CI): FDA-test: continued improvement at each stage. Able to attend normal kindergarten, normal dialogue possible, PPC. Patient 2: FDA-test: improved at every stage, perfect score at 12 months. At 24 months: first adult test (FMT+HSM): speech tracking (ST) 54.8, monosyllabic 25%, numbers (N) 50%, PPC, at 8 years, f/u- attends normal school, satisfactory academic performance. Patient 3 (bimodal): FDA-test: good at first fitting, great at 3 months, FMT+HSM at 12 months:ST 31.6, MS 5%, N 70%, PCC, at 24 months: ST 31.8, MS 25%, N 70%, HSMs 48.1%, PPC. At 9 years f/u: ST54.8, MS 40%, N 80%, HSM-s: 75.5%, HSM-10 21.2%. Patient 4: FMT+HSM at first fitting, 3 months, 12 months, 24 months, and 3 years (respectively): ST: 29.4%, 30.8%, 29.4%, 79.4%, 87.73%. MS: 25%, 35%, 25%, 40%, 50%. N: 80%, 95%, 80%, 90%, 100%. HSM-s: 8.4%, 57.5%, 8.4%, 79%, 87.7%. Patient 5: FMT+HSM at first fitting, 3 months, and 12 months: ST: 57.8, 68.2, 78.8. MS: n/a, 75%, 75%. N: n/a, 100%, 100%. HSM-s: n/a, 85.84%, 98.11%, HSM-10: n/a, n/a, 7.54% | | |
| Study                        | Preoperative data                                                                 | Postoperative data                                                                 | Overall benefit (subjective assessment) | Follow-up |
|-----------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------|-----------|
| Kuthubutheen et al.         | Ling Sounds:                        | Ling Sounds: 24 h: 250 Hz: 80 dB, 500 Hz: 105 dB, 750 Hz: 110 At 12 months: 500 Hz: 100 dB, 1 kHz: 115 dB. | Hearing preservation effective and outcomes good | 12 months |
| Loundon et al.              | Not reported                        | Speech perception scores: OSW at 12 months: mean 75.9 (10-100), OSW at 24 months: mean 83 (40-100). Language at 12 months: simple sentences (n=5), complex sentence (n=2), isolated words (n=2), non-grammatical sentences (n=1), no speech (n=1). Language at 24 months: simple sentences (n=3), complex sentence (n=5), isolated words (n=6), non-grammatical sentences (n=2), no speech (n=1). | Good outcomes in perception and linguistics | 24 months |
| Mikkelsen et al.            | Pure-tone audiometry: PTA average of 0.5, 1, 2, and 4 kHz = right 51/ left 58, air-bone gap presents at lower frequencies. | Peabody Picture Vocabulary Test At 6 months: good self-reported hearing, PPVT receptive language acquisition age 5.4 (chronological age 10.1) with CI+HA. Requires daily speech training at 6 months. | Good result post implant. EES/EVA not a contraindication for CI. | 6 months  |
| Park et al.                 | Pure-tone audiometry: Group 1 (SLC26A4): CAP 2.8 (0.6) IT-MAIS 23.6 (6.3) Group 2 (Genetic other): CAP 0.2 (0.2), IT-MAIS 5.5 (1.8), Group 3 (Non-genetic, no inner-ear anomaly): CAP 0.4 (0.3), IT-MAIS 5.5 (1.8), Group 4 (non-genetic with inner-ear anomaly): CAP 0 (0), IT-MAIS 0.5 (0.3). Speech perception scores: | Pure-tone audiometry: Group 1: Subgroup early CI (<24 months) (n=2): CAP at 3, 6, 12, 18 and 24 months: 3.0 (0.0), 4.0 (0.0), 5.0 (0.0), 6.0 (0.0), 7.0 (0.0). Group late CI (>24 months) (n=7): CAP at 3, 6, 12, 18, and 24 months: 4.0 (0.2), 4.9 (0.4), 5.9 (0.3), 6.1 (0.4), 6.7 (0.2). In age-adjusted analysis, Group 1 had higher CAP scores than the other 3 subgroups at baseline and at all time points post-CI. Post-CI longitudinal change of CAP scores was greater in group 1 than in group 2 (P=0.001), group 3 (P=0.045), and group 4 (P<0.001). Speech perception scores: | Genetically diagnosed cochlear implantees show better functional outcomes after CI than undiagnosed cochlear implantees | 24 months |
| Roh et al.                  | Pure-tone audiometry: PTA (R/L) and PTA-low (R/L) dB HL: Patient 1 (m): 87/96 & 65/83, Patient 2: 104/87 & 85/72, Patient 3: 94/so & 70/so, Patient 4 (m): 101/99 & 97/97, Patient 5 (m): 98/117 & 80/so, Patient 6: 77/73 & 72/65, Patient 7: 99/102 & 82/93, Patient 8 (m): 108/108 & 90/100. **Patients with Mondini labeled as (m). Low-frequency thresholds = 0.25, 0.5, and 1 kHz. | Pure-tone audiometry: All patients showed preserved hearing after implantation. On average, the threshold change across frequencies was; 0.25 kHz: 9±11 dB, 0.5 kHz: 6±13 dB, 1 kHz: 9±18 dB, 2 kHz: 11±11 dB, 3 kHz: 9±11 dB, 4 kHz: 6±9 dB. Average hearing deterioration was 8.75 dB (0–26.67). Average hearing deterioration for low tones (at 0.25, 0.5, and 1 kHz) was 8.1 dB (5–20). One patient (patient 6) showed deterioration of >15 dB. PTA-low were maintained until follow-up at 18 months. **postoperative PTA conducted without the aid of the cochlear implant to assess hearing preservation. 6/8 preferred EAS mode to electrical alone mode, 3/4 patients showed better performance with EAS mode than electrical alone in the monosyllable test. | Preservation of residual hearing could be achieved after CI in patients with SLC26A4 mutations and most patients benefited from electrophysiological stimulation in speech understanding in both quiet and noisy conditions | 18 months |
### Table 2. Summary of audiological outcomes

| Study             | Preoperative data                                                                 | Postoperative data                                                                 | Overall benefit (subjective assessment) | Follow-up |
|-------------------|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------|-----------|
| Steinbach et al.  | Age 16 m: Right profound HL, Left mixed moderate with conductive HL 15–20 dB Age 18: Bilateral profound SNHL, R ear (with HA)- 25%-word discrimination at 65 dB, 0% in L ear (with HA), 20% with B/L HA (Freiburg monosyllable testing). Preoperation: HSM sentences without noise <1%, HSM sentences with 10-dB SNR <1% | HSM sentences: 7 weeks postimplant: 27% (without noise), 4% (with 10-dB noise). 0 months postimplant: 86.8% (without noise), 138.7% (with 10-dB noise) | CI performed with good results | 10.5 months |
| Sweetow et al.    | Word recognition testing (WRT): Age 5: 60% R, 78% L (NU-CHIPS stimuli), aided 68% (WPI stimuli) Age 10: 40% R, 52% L (PBK-50 stimuli), aided R 64%, aided L 68% (WPI stimuli) Age 11: 36% R, 44% L (PBK-50 stimuli), aided 44% (PBK-50 stimuli), Age 12: 24% R, 16% L (PBK-50 stimuli) PTA: 80–105dB HL (preoperatively) | WRT: Age 13: 18% (PBK-90 stimuli) Age 14 (CI+ HA): 60% (PBK-50) PTA: Warble tone thresholds 30–40 dB | Useful benefit from implantation | 12 months |
| Vaisbuch et al.   | Implanted ear- AzBio sentences (60 dB): 12% Nonimplanted ear-WRS (100 dB): 24%, PTA (bone conduction): 20 dB at 0.5 kHz, 20 dB at 1 kHz | Implanted ear- AzBio sentences (60 dB): 63% at 4 weeks, 70% at 6 months Nonimplanted ear- Word recognition scores (100 dB): 8% at 2 weeks, 8% at 6 months, PTA (bone conduction): 25 dB at 0.5 kHz, 95 dB at 1 kHz (2 weeks), 15 dB at 0.5 kHz, 40 dB at 1 kHz (6 months) | Improved hearing in implanted ear; however, sudden, progressive SNHL on contralateral side immediately postoperatively | 6 months |
| van Nierop et al. | Adult (aided) phoneme score (SD) (n=7): 15% (15) in PS, 23% (18) reference group, 28% (22) in EVA (non-PS). Child (aided) phoneme score (SD) (n=21): 35%(24) in PS, 37%(22) in reference group, 63%(35) in EVA (non-PS) | Adult (aided) phoneme score (SD) (n=7): PS group: 63.6% at 6 months, 81.0% at 12 months. Age-adjusted adult mean phoneme at 12 months: EVA: 66%, reference group 73%, PS 78%. Child (aided) phoneme score (SD) (n=21): PS group: 85.7% (6 months), 86.9% (12 months), 87.4% (24 months), 89.9% (48 months), 92.8% (>48 months) Age-adjusted mean phoneme at 36 months: EVA 84%, reference group 79%, PS 91%. | Clear benefits in speech perceptions and QOL in PS. No difference between PS and non-PS EVA | 12 months |
| Wu et al.         | PTA (dB): 98.7                                                                   | SRS: Consonant 88.0%, vowel 86.2%, tone 91.7%, PB word 79.2%, sentence 89.9%         | Children with either SLC26A4 or GJB2 mutations excelled in speech perception performance after cochlear implantation | 3.7 years |
| Wu et al.         | Not reported                                                                     | PTA (Residual hearing, dB): Total (n=22): 97.5±11.0, 1 mutation subgroup (n=4): 96.3±8.5, 2 mutation subgroup (n=18): 97.7±10.4 CAP (at 3 years): Total: 6.8±0.4, 1 mutation subgroup: 6.0±0, 2 mutation subgroup 6.7±0.5 | Good performance post implantation | 3 years |
| Wu et al.         | CI before 3.5 years (n=6): CAP 2, SIR 1, CI after 3.5 years (n=17): CAP 4, SIR 3 | CI before 3.5 years old (n=6): CAP 6 at 3 years, 7 at 5 years. SIR 4.5 at 3 years, 5 at 5 years. Easy sentence at 3 years: 98.0±2.8. CI after 3.5 years old (n=17): CAP 6 at 3 years, 7 at 5 years. SIR 5 at 3 years, 5 at 5 years. Easy sentence at 3 years: 83.1±29.6. | GJB2 and SLC26A4 mutations were associated with good postimplant outcomes. However, their effect on CI outcomes was modulated by the age at implantation and the duration of implant use | 5 years |
Audiological Outcomes

Audiological outcomes are summarized in Table 2. A total of 25 different audiological outcome measures were used, and there was inconsistency with the use of pre- and postoperative reporting across the included studies. Pure-tone audiometry (PTA) was recorded in 5 studies preoperatively and in 6 studies both pre- and post-procedure. Speech intelligibility was assessed in 3 studies, using the Speech Intelligibility Rating, both pre- and postimplantation. Speech reception was assessed in 22 studies through a variety of means; 7 studies used categories of auditory performance (CAP) to assess the postoperative performance, 6 of which also used CAP score preoperatively. Phoneme scores were used to assess receptive language after implantation in 3 studies. Other outcomes assessing speech perception included the listening progress profile, word recognition score, Japanese Infant Word Discrimination Test, Geers and Moog Speech Reception Score, AzBio Sentence test, Open-Set Monosyllabic word, and the Parents’ evaluation of aural/Oral Performance of Children scale. Furthermore, 1 study assessed patients’ quality of life (QoL) using the Nijmegen cochlear implant questionnaire both pre- and postoperatively.[39]

Overall, there was a trend toward patients obtaining benefit postimplantation regardless of the assessment method used. Reporting was heterogeneous with respect to duration of follow-up as well as methods of assessment. Of the 22 studies, 19 reported on preimplantation hearing outcomes, which were typically severe to profound deficits. All studies reported improved auditory/speech and language performance, although this was rarely reported with statistical testing.

Surgical Outcomes

A total of 10 studies reported on intra- or postoperative complications. A total of 46 complications were reported in 78 patients, none of which were major. The release of CSF was the most common intraoperative complication, accounting for 42/46 minor complications. Intraoperatively, this was managed with either no intervention, soft tissue plugging at the cochleostomy, or anti-Trendelenburg positioning. Moreover, 1 patient required a lumbar drain, which was removed on day 2 postoperatively.[39] The other minor complications reported included nausea and vomiting (n=2), mild dizziness and imbalance (n=1), and a mild lip swelling treated with antihistamines (n=1).

Quality of Studies

The methodological quality of included studies was modest, predominately consisting of cohort studies of limited design, case reports, and non-controlled case series with a small number of patients. All studies were OCEBM grade III-IV (Table 1); 4 studies were prospective, and the remaining studies were retrospective. Heterogeneity of audiological outcomes precluded a meta-analysis. There were also limitations in reporting of implant used, surgical technique, and rehabilitation protocols. In total, 3 studies were included by the same authors from 2 CI units; therefore, it is possible that there is some duplication of included patients.[21,27,28]

DISCUSSION

CLINICAL AND RESEARCH CONSEQUENCES

This systematic review and narrative synthesis reports on the outcomes of cochlear implantation in profoundly deaf children diagnosed with Pendred syndrome. To the authors’ knowledge, this is the first systematic review on this topic. Good audiological outcomes were described in the majority of included studies for patients with SLC26A4 mutations or clinically diagnosed Pendred syndrome. All studies that assessed speech intelligibility showed improvements in linguistic ability[27,22,40], and QoL reported by Van Nierop et al. demonstrated excellent performance after implantation[12].

Owing to the nature of Pendred syndrome, the diagnostic criteria used among the included studies were variable. All the patients presented with severe to profound sensorineural hearing loss (SNHL) with either radiological characteristics or with genetically confirmed SLC26A4 mutations. Analysis of audiological outcomes related to radiological findings was not possible. Moreover, 5 studies did not report a radiological assessment of the preoperative anatomy, and only 1 study reported individual data on the presence of a Mondini malformation and residual PTA thresholds.[26]. Demir et al.[32] studied the relationship between vestibular aqueduct diameter and audiological outcomes with no significant relationships identified. This is reflected in the literature with no identified impact of inner-ear malformations on long-term CI outcomes.[41]. In addition, patients with nonspecified EVA (and no genetic analysis) had superior outcomes with CI than those with normal anatomy[32,40].
Van Nierop et al. considered that patients with confirmed Pendred syndrome and those with nonsyndromic EVA could be considered comparable with regard to preoperative counseling on likely audito-
ry performance. This is in contrast to the work by Colvin et al., who found patients with Pendred syndrome to have a worse audiological prognosis compared with those with isolated EVA.

In a number of studies, the authors compared CI performance with other patient groups. Broomfield et al.[6] showed patients with Pendred syndrome to have comparable audiological performance after CI compared with other patients with a genetic hearing loss; how-
ever, the outcomes varied both within and between the syndromic groups. Although both the genetic groups had excellent audiological outcomes, patients with SLC26A4 mutations were found to perform inferiorly to those possessing GJB2 mutations.[21,23,27] Several studies demonstrated children possessing SLC26A4 mutations to have better outcomes than those with genetically undiagnosed hearing loss.[12,21,24,27] Wu et al. theorized that as part of the phenotypic picture, the genetic consequences in Pendred syndrome are limited to the inner ear, sparing the auditory nerve and central auditory pathways.[21]. Consequently, candidates who can expect excellent outcomes from CI may be identified by isolating those with syndromes that exclu-
sively affect the inner ear. The value of genetically screening the pa-
tients before implantation was emphasized in many studies.[6,24,26,33,36]. In several studies, the optimum age of implantation was discussed. The significant improvements in postimplantation audiological performance in patients with SLC26A4 or GJB2 mutations versus patients without mutations were only statistically significant in pa-
tients receiving their CI before the age of 3.5 years.[27] Furthermore, Govaerts et al.[42] reported better audiological outcomes in children who underwent implantation before the age of 2 years, with a greater chance of attaining age-appropriate CAP scores in the immediate postoperative period. Nicolas and Geers also found 2 years as the cutoff for optimum CI results and found an association with poorer CAP scores for children who received the implant over the age of 2 years.[43].

In patients experiencing a fluctuant pattern of hearing loss, the de-
cision becomes more challenging. Owing to the unstable nature of patients with fluctuating hearing loss, some parents are hesitant for surgical management when the possibility of spontaneous improve-
ment exists.[46] Sweetow et al.[22] described the potentially “tragic error” of a child losing their residual hearing as a result of premature implantation for a child who may have recovered to a level at which they may benefit from hearing aids. They did, however, appreciate the emotional and developmental impact, which may be incurred by delaying, and reasoned that hybrid implants may be the preferred approach for fluctuant presentations. Gratacap and Mikkelsen con-
cluded that cochlear implantation should not be delayed in children with fluctuating hearing loss owing to the effect on speech and language development.[16,38]. In fact, it has been argued that the fluctu-
ating pattern of hearing loss is in itself an indication to avoid delay.[44]. Ko et al.[46] recommended that patients do not need to wait until the hearing threshold exceed 90-dB HL to benefit from CI, especially if they failed to recover their auditory function after 3 months. They also warned against snapshot assessments of auditory performance, such as CAP and phonetically balanced word test, in patients with unstable or fluctuating hearing loss, with preference for speech intel-
ligibility and perception tools.

Other considerations that were discussed included the use of imaging to plan and avoid complications. This was particularly found to be the case for surgical planning in patients presenting with EES.[38]. Kontorinis et al.[20] found minor surgical challenges in patients with inner-ear malformations, which resulted in longer operating times. The value of radiological investigations to aid diagnosis and implan-
tation has been emphasized by several authors, particularly alongside genetic testing.[21,31,37,38]. In 2 studies of patients with EVA and ESS, conductive hearing loss was reported.[29,38]. According to Nakashima et al.[45] it is common for patients with Pendred syndrome or nonsyn-
dromic EVA to present with an air-bone gap without any middle-ear pathology. The precise mechanism is not fully understood; how-
ever, a theory suggests that a “third window” may result from an EVA and ESS presenting as mixed hearing loss with a fluctuating pattern.[46]. This can also occur without ESS via the proposed mechanism of acoustic energy being shunted away from the cochlea.[47].

Inner-ear malformations were once considered a contraindication to cochlear implantation, with the first reported successful procedure in 1983 on a patient with Mondini dysplasia.[46]. The most common complication described in the literature is the CSF “gusher,” a term describing the egress of clear fluid upon cochleostomy.[48]. The termin-
ology used in our included studies was variable, describing a range of CSF and perilymph leaks, and gushers. The inner ear contains no more than a few microliters of perilymph; therefore, the term peri-
lymph gusher can be considered a misnomer.[50] Furthermore, Pa-
psin[41] argued that only pulsatile leaks of CSF for over 1 min should be classified as “gushers,” suggesting that there may be an overes-
timation in the literature. There is a theoretical risk of developing otogenic meningitis as a consequence of abnormal communication between CSF and perilymph in the cochlea.[49,51].

In our review, intraoperative CSF leak was described in 46 of 231 pa-
tients, with no reports of meningitis. Auditory outcomes were not described in relation to CSF gusher in the included studies; however, Adunke et al.[52] approached this topic and found no association between the two. Although a wider horizontal width of the vestibular aqueduct has been associated with greater risk of CSF gusher; there-
fore, radiological assessment is recommended.[31,53]. No major adverse events were recorded in any of the studies included in our review. Conversely, it was reported in 2 excluded studies.[35,54] that 1 patient experienced vertigo for over 6 months and the other had severe imbalance and vomiting, which resulted in severe hypokalemia and multiple cardiac arrests. The latter patient recovered and subsequently became a good CI user. The case presented by Vaisbuch et al.[35] is notable be-
cause an adult with bilateral EVA experienced sudden contralateral SNHL upon implantation, with partial recovery. The authors believe that this occurred as a result of the CSF gusher or lumbar drain inser-
tion, causing changes in the intracranial CSF volume. A recommenda-
tion has been made that patients are adequately counseled about the risk of postoperative SNHL in the nonimplanted ear.

CONCLUSION

Hearing outcomes after CI in Pendred syndrome are generally good with the majority of patients experiencing a benefit in terms of both
speech perception and speech intelligibility. A significant number of patients experienced CSF release intraoperatively; however, major complications were rare. Radiological assessment and genetic analysis, where possible, aid in both diagnosis and surgical planning for patients undergoing cochlear implantation. Owing to the variable phenotypic presentation, deciding to time of implantation remains a challenge; therefore, CI teams must use their experience to clinically weigh the benefits to each patient.

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REFERENCES
1. Kopp P, Bizhanova A. Clinical and molecular characteristics of Pendred syndrome. Ann Endocrinol 2011; 72: 88-94. [Crossref]
2. Pendred V. Deaf-Mutism and Goitre. The Lancet 1896; 148: 532. [Crossref]
3. Coyle B, Coffey R, Armour JA, Gausden E, Hochberg Z, Grossman A, et al. Pendred syndrome (goitre and sensorineural hearing loss) maps to chromosome 7 in the region containing the nonsyndromic deafness gene DFNB4. Nat Genet 1996; 12: 421-3. [Crossref]
4. Sheffield VC, Kraitham Z, Beck JC, Nishimura D, Stone EM, Salameh M, et al. Pendred syndrome maps to chromosome 7q21-34 and is caused by an intrinsic defect in thyroid iodine organification. Nat Genet 1996; 12: 424-6. [Crossref]
5. Wémeau JL, Kopp P. Pendred syndrome. Best Pract Res Clin Endocrinol Metab 2017; 31: 213-24. [Crossref]
6. Everett LA, Glaser B, Beck JC, Idol JR, Buchs A, Heyman M, et al. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). Nat Genet 1997; 17: 411-22. [Crossref]
7. Reardon W, Coffey R, Phelps PD, Luxon LM, Stephens D, Kendall-Taylor P, et al. Pendred syndrome—100 years of underascertainment? QJM Mon J Assoc Physicians 1997; 90: 443-7. [Crossref]
8. Batsakis JG, Nishiyama RH. Deafness with sporadic goiter. Pendred’s syndrome. Arch Otolaryngol Chic Ill 1960. 1962; 76: 401-6. [Crossref]
9. Gettellfinger JD, Dahl JP. Syndromic Hearing Loss: A Brief Review of Common Presentations and Genetics. J Pediatr Genet 2018; 7: 1-8. [Crossref]
10. Phelps PD, Coffey RA, Trebath RC, Luxon LM, Grossman AB, Britton KE, et al. Radiological malformations of the ear in Pendred syndrome. Clin Radiol 1998; 53: 268-73. [Crossref]
11. Bizhanova A, Kopp P. Genetics and phenomics of Pendred syndrome. Mol Cell Endocrinol 2010; 322: 83-90. [Crossref]
12. van Nierop JW, Huinck WJ, Pennings RJE, Admiraal RJC, Mylanus EAM, Kunst HPM. Patients with Pendred syndrome: is cochlear implantation beneficial? Clin Otolaryngol 2016; 41: 386-94. [Crossref]
13. Pryor SP, Madoe AC, Reynolds JC, Sarliss NJ, Arinos KS, Nance WE, et al. SLC26A4/PDS genotype-phenotype correlation in hearing loss with enlargement of the vestibular aqueduct (EVA): evidence that Pendred syndrome and non-syndromic deafness are distinct clinical and genetic entities. J Med Genet 2005; 42: 159-65. [Crossref]
14. Farrior JB, Endicott JN. Congenital mixed deafness: cerebrospinal fluid otorrhea. Ablation of the aqueduct of the cochlea. The Laryngoscope 1971; 81: 684-99. [Crossref]
15. Blamey P, Artieres F, Başkent D, Bergeron F, Beynon A, Burke E, et al. Factors affecting auditory performance of postlingually deaf adults using cochlear implants: an update with 2251 patients. Audiol Neurotol 2013; 18: 36-47. [Crossref]
16. Brazzelli M, Cuiickshank M, Tassie E, McNamee P, Robertson C, Elders A, et al. Collagenase clostripid histolyticum for the treatment of Dupuytren’s contracture: systematic review and economic evaluation. Appendix 4 Risk-of-bias checklist: non-randomised comparative studies. Health Technol Assess Winch Engl 2015; 19: 1-202. [Crossref]
17. OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2. Oxford Centre for Evidence-Based Medicine; Available from: https://www.cebm.net/index.aspx?o=5653
18. Moher D, Liberati A, Tetzlaff J, Altmann DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264-9, W64. [Crossref]
19. Kuthubutheen J, Hedne CN, Krishnaswamy R, Rajan GP. A case series of paediatric hearing preservation cochlear implantation: a new treatment modality for children with drug-induced or congenital partial deafness. Audiol Neurotol 2012; 17: 321-30. [Crossref]
20. Kontorinis G, Lenarz T, Lesinski-Schiedat A, Neuberger J. Cochlear implantation in Pendred syndrome. Cochlear Implants Int 2011; 12: 157-63. [Crossref]
21. Wu CC, Liu TC, Wang SH, Hsu CJ, Wu CM. Genetic characteristics in children with cochlear implants and the corresponding auditory performance. The Laryngoscope 2011; 121: 1287-93. [Crossref]
22. Sweetow RW, Rosse KW, Philipposian C, Miller MT. Considerations for cochlear implantation of children with sudden, fluctuating hearing loss. J Am Acad Audiol 2005; 16: 770-80. [Crossref]
23. Yan Y, Li Y, Yang T, Huang Q, Wu H. The effect of GJB2 and SLC26A4 gene mutations on rehabilitation outcomes in pediatric cochlear implant patients. E Eur Arch Otorhinolaryngol 2013; 270: 2865-70. [Crossref]
24. Park JH, Kim AR, Han JH, Kim SD, Kim SH, Koo JW, et al. Outcome of Cochlear Implantation in Prelingually Deafened Children According to Molecular Genetic Etiology. Ear Hear 2017; 38: e316-24. [Crossref]
25. Chiong CM, Reyes-Quintos MaRT, Zarca T KL, Tobias-Grasso CAM, Acharaya A, Leal SM, et al. The SLC26A4 c.706C>G (p.Leu236Val) variant is a frequent cause of hearing impairment in Filipino cochlear implantees. Otol Neurotol 2018; 39: e726-30. [Crossref]
26. Roh KJ, Park S, Jung JS, Moon IS, Kim SH, Bang MY, et al. Hearing Preservation During Cochlear Implantation and Electroacoustic Stimulation in Patients With SLC26A4 Mutations. Otol Neurotol 2017; 38: 1262-7. [Crossref]
27. Wu CM, Ko HC, Tsou YT, Lin HY, Lin JL, Chen CK, et al. Long-Term Cochlear Implant Outcomes in Children with GJB2 and SLC26A4 Mutations. PLoS One 2015 10: e0138575. [Crossref]
28. Wu CC, Lee VC, Chen PJ, Hsu CJ. Predominance of genetic diagnosis and imaging results as predictors in determining the speech perception performance outcome after cochlear implantation in children. Arch Pediatr Adolesc Med 2008; 162: 269-76. [Crossref]
29. Steinbach S, Brockmeier SJ, Kiefer J. The large vestibular aqueduct—case report and review of the literature. Acta Otolaryngol (Stockh) 2006; 126: 788-95. [Crossref]
30. Gratacap M, Thierry B, Rouillon I, Marlin S, Garabedian N, Louidon N. Pediatric cochlear implantation in residual hearing candidates. Ann Otol Rhinol Laryngol 2015; 124: 443-51. [Crossref]
31. Yamazaki H, Naito Y, Moroto S, Tamaya R, Yamazaki T, Fujiwara K, et al. SLC26A4 pThr410Met homozygous mutation in a patient with a cystic renal dysplasia. J Med Genet 2005; 42: 339-42. [Crossref]
32. Demir B, Cesur S, Incaz S, Alberalard NA, Ciprut A, Batman C. The effect of canal diameter on audiologic results in patients with cochlear implantation with large vestibular aqueduct syndrome. Eur Arch Oto-Rhino-Laryngol 2020; 277: 743-50. [Crossref]
33. Fahy CP, Carney AS, Nikolopoulos TP, Ludman CN, Gibbin KP. Cochlear implantation in children with large vestibular aqueduct syndrome and a review of the syndrome. Int J Pediatr Otorhinolaryngol 2001; 59: 207-15. [Crossref]

34. Loundon N, Rouillon I, Munier N, Marlin S, Roger G, Garabedian EN. Cochlear implantation in children with internal ear malformations. Otol Neurotol 2005; 26: 668-73. [Crossref]

35. Vaisbuch Y, Thai A, Pirko SL, Santa Maria PL. Sensorineural Hearing Loss in the Nonimplanted Ear Following Cochlear Implantation in a Patient With Bilateral Enlarged Vestibular Aqueducts. Otol Neurotol 2019; 40: e782-6. [Crossref]

36. Broomfield SJ, Bruce IA, Henderson L, Ramsden RT, Green KMJ. Cochlear implantation in children with syndromic deafness. Int J Pediatr Otorhinolaryngol 2013; 77: 1312-6. [Crossref]

37. de Wolf MJF, Honings J, Joosten FBM, Hoefsloot L, Mylanus E a. M, Cremers CWRJ. Two siblings with progressive, fluctuating hearing loss after head trauma, treated with cochlear implantation. J Laryngol Otol 2010; 124: 86-9. [Crossref]

38. Mikkelsen KS, Tranebjærg L, Mey K. Cochlear implantation in a 10-year old boy with Pendred syndrome and extremely enlarged endolymphatic sacs. Cochlear Implants Int 2019; 20: 100-3. [Crossref]

39. van Nierop JW, Huinck WJ, Pennings RJ, Admiraal RJ, Mylanus EA, Kunst HP. Patients with Pendred syndrome: is cochlear implantation beneficial? Clin Otolaryngol 2016; 41: 386-94. [Crossref]

40. Ko HC, Liu TC, Lee LA, Chao WC, Tsou YT, Ng SH, et al. Timing of surgical intervention with cochlear implant in patients with large vestibular aqueduct syndrome. PLoS One 2013; 8: e81568. [Crossref]

41. Papsin BC. Cochlear implantation in children with anomalous cochleovestibular anatomy. The Laryngoscope 2005; 115: 1-26. [Crossref]

42. Govaerts PJ, De Beukelaer C, Daemers K, De Ceulaer G, Somers T, et al. Outcome of cochlear implantation at different ages from 0 to 6 years. Otol Neurotol 2023; 23: 885-90. [Crossref]

43. Nicholas JG, Geers AE. Will They Catch Up? The Role of Age at Cochlear Implantation In the Spoken Language Development of Children with Severe-Profound Hearing Loss. J Speech Lang Hear Res 2007; 50: 1048-62. [Crossref]

44. Mori T, Westerberg BD, Atashband S, Kozak FK. Natural history of hearing loss in children with enlarged vestibular aqueduct syndrome. J Otolaryngol 2008; 37: 112-8.

45. Nakashima T, Ueda H, Furuhashi A, Sato E, Asahi K, Naganawa S, et al. Air-bone gap and resonant frequency in large vestibular aqueduct syndrome. Am J Otol 2000; 21: 671-4.

46. Seo YJ, Kim J, Choi JY. Correlation of vestibular aqueduct size with air-bone gap in enlarged vestibular aqueduct syndrome. The Laryngoscope 2016; 126: 1633-8. [Crossref]

47. Merchant SN, Nakajima HH, Halpin C, Nadol JB, Lee DJ, Innis WP, et al. Clinical Investigation and Mechanism of Air-Bone Gaps in Large Vestibular Aqueduct Syndrome. Ann Otol Rhinol Laryngol 2007; 116: 532-41. [Crossref]

48. Mangabeira-Albernaz PL. The Mondini dysplasia--from early diagnosis to cochlear implant. Acta Otolaryngol (Stockh) 1983; 95: 627-31. [Crossref]

49. Sennaroglu L. Cochlear implantation in inner ear malformations--a review article. Cochlear Implants Int 2010; 11: 4-41. [Crossref]

50. Janssens S, Govaerts PJ, Casselman J, Van Rompaey W, Van Langenhove A, Somers T, et al. The LAURA multichannel cochlear implant in a true Mondini dysplasia. Eur Arch Oto-Rhino-Laryngol 1996; 253: 301-4. [Crossref]

51. Terry B, Kelt RE, Jeyakumar A. Delayed Complications After Cochlear Implantation. JAMA Otolaryngol--Head Neck Surg 2015; 141: 1012-7. [Crossref]

52. Adunka OF, Teagle HFB, Zdanski CJ, Buchman CA. Influence of an intraoperative perilymph gusher on cochlear implant performance in children with labyrinthine malformations. Otol Neurotol 2012; 33: 1489-96. [Crossref]

53. Kamogashira T, Iwasaki S, Kashio A, Kakigi A, Karino S, Matsumoto Y, et al. Prediction of Intraoperative CSF Gusher and Postoperative Facial Nerve Stimulation in Patients with Cochleovestibular Malformations Undergoing Cochlear Implantation Surgery. Otol Neurotol 2017; 38: 114-9. [Crossref]

54. Sanei-Moghaddam A, Wilson T, Kumar S, Gray R. An unfortunate case of Pendred syndrome. J Laryngol Otol 2011; 125: 965-7. [Crossref]