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 organization, 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 intercalar 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 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. Moreover, 13 studies reported a genetic analysis for included patients, reporting a range of mutations in the SLC26A4/PDS gene. 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.

Figure 1. PRISMA Flowsheet showing study identification process

Table 1. Study characteristics

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

*Oxford Centre for Evidence-Based Medicine
<table>
<thead>
<tr>
<th>Study</th>
<th>Preoperative data</th>
<th>Postoperative data</th>
<th>Overall benefit (subjective assessment)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broomfield et al.</td>
<td>Not reported</td>
<td>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</td>
<td>Good outcomes in PS. Cognition may influence success of CI</td>
<td>68 months</td>
</tr>
<tr>
<td>De Wolf et al.</td>
<td>Pure-tone audiometry: Sibling 1: (age 4.2 years): 63 dB (right), 77 dB (left), age 5.5 years: &gt;110 dB (right), 90 dB (left) 75% at 95 dB with hearing aid in left ear. Sibling 2: Fletcher index 90 dB (right), 55 dB (left), with BL hearing aids: Speech perception scores: Phoneme score 75% at 70 dB, left only: 9% speech recognition, Right 54%.</td>
<td>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)</td>
<td>CI is successful despite cochlear hypoplasia</td>
<td>2–24 months</td>
</tr>
<tr>
<td>Demir et al.</td>
<td>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).</td>
<td>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). Improvements in all parameters from pre- to post operation were statistically significant</td>
<td>Patients with LVAS benefit from CI</td>
<td>x</td>
</tr>
<tr>
<td>Gratacap et al.</td>
<td>Pure-tone audiometry: Preoperative mean: nonaided PTA threshold: mean 101, median 100 (87–117), aided PTA threshold: mean 67, median 63 (42–105),</td>
<td>Speech perception scores: OSW at 12 months: mean 74, median 82 (10–100), OSW at 24 months: mean 81, median 90 (40–100)</td>
<td>Good performance with CI (no subgroup analysis by etiology)</td>
<td>24 months</td>
</tr>
<tr>
<td>Study</td>
<td>Preoperative data</td>
<td>Postoperative data</td>
<td>Overall benefit (subjective assessment)</td>
<td>Follow-up</td>
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<tr>
<td>Ko et al.</td>
<td>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)</td>
<td>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 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).</td>
<td>High levels of speech performance are reached after 5 years of implant use in patients with LVAS</td>
<td>5.8 years</td>
</tr>
<tr>
<td>Kontorinis et al.</td>
<td>Pure-tone audiometry: Patients 1 and 2: no data, patient 3: PTA 100 dB (right), 90 dB (left), Patient 4: PTA 80 dB (right), 70 dB (left), AEP 80 dB (left), 80 dB (right), Patient 5: PTA 80 dB (left), promontory test positive (left)</td>
<td>Speech perception scores: 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%.</td>
<td></td>
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<tr>
<td>Study</td>
<td>Preoperative data</td>
<td>Postoperative data</td>
<td>Overall benefit (subjective assessment)</td>
<td>Follow-up</td>
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<tr>
<td>Kuthubutheen et al.</td>
<td>Ling Sounds: Ling Sound (because of age and language delay) 250 Hz:50 dB, 500 Hz: 50 dB, 1 kHz:55 dB, 2 kHz: 50 dB, 3 kHz: 85 dB, 4 kHz: 95 dB</td>
<td>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.</td>
<td>Hearing preservation effective and outcomes good</td>
<td>12 months</td>
</tr>
<tr>
<td>Loundon et al.</td>
<td>Not reported</td>
<td>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=0), non-grammatical sentences (n=2), no speech (n=1).</td>
<td>Good outcomes in perception and linguistics</td>
<td>24 months</td>
</tr>
<tr>
<td>Mikkelsen et al.</td>
<td>Pure-tone audiometry: PTA average of 0.5, 1, 2, and 4 kHz = right 51/ left 58, air-bone gap presents at lower frequencies.</td>
<td>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.</td>
<td>Good result post implant. EES/EVA not a contraindication for CI.</td>
<td>6 months</td>
</tr>
<tr>
<td>Park et al.</td>
<td>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 5.1 (1.8), Group 4 (non-genetic with inner-ear anomaly): CAP 0 (0), IT-MAIS 0.5 (0.3) Speech perception scores: Group 1: Subgroup early CI (&lt;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), 5.5 (0.5). Subgroup late CI (&gt;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&lt;0.001). Speech perception scores:</td>
<td>Genetically diagnosed cochlear implanters show better functional outcomes after CI than undiagnosed cochlear implanters</td>
<td>24 months</td>
<td></td>
</tr>
<tr>
<td>Roh et al.</td>
<td>Pure-tone audiometry: PTA (R/L) and PTA-low (R/L) dB HL: Patient 1 (m): 87/96 &amp; 65/83, Patient 2: 104/87 &amp; 85/72, Patient 3: 94/so &amp; 70/so, Patient 4 (m): 101/99 &amp; 97/97, Patient 5 (m): 98/117 &amp; 80/so, Patient 6: 77/73 &amp; 72/65, Patient 7: 99/102 &amp; 82/93, Patient 8 (m): 108/108 &amp; 90/100, Patients with Mondini labeled as (m). Low-frequency thresholds= 0.25, 0.5, and 1 kHz.</td>
<td>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+-/8 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 (0.25, 0.5, and 1 kHz) was 8.1 dB (5–20). One patient (patient 6) showed deterioration of &gt;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.</td>
<td>Preservation of residual hearing could be achieved after CI in patients with SLC26A4 mutations and most patients benefited from electroacoustic stimulation in speech understanding in both quiet and noisy conditions</td>
<td>18 months</td>
</tr>
</tbody>
</table>
Table 2. Summary of audiological outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Preoperative data</th>
<th>Postoperative data</th>
<th>Overall benefit (subjective assessment)</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinbach et al.</td>
<td>Age 16 m: Right profound HL, Left mixed moderate with conductive HL 15–20 dB</td>
<td>HSM sentences: 7 weeks postimplant: 27% (without noise), 4% (with 10-dB noise).</td>
<td>CI performed with good results</td>
<td>10.5 months</td>
</tr>
<tr>
<td></td>
<td>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).</td>
<td>0 months postimplant: 86.8% (without noise), 138.7% (with 10-dB noise).</td>
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<td></td>
<td>Preoperation: HSM sentences without noise &lt;1%, HSM sentences with 10-dB SNR &lt;1%</td>
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<td>Sweetow et al.</td>
<td>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)</td>
<td>WRT: Age 13: 18% (PBK-90 stimuli) Age 14 (CI+ HA): 60% (PBK-50) PTA: Warble tone thresholds 30–40 dB</td>
<td>Useful benefit from implantation</td>
<td>12 months</td>
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<tr>
<td>Vaisbuch et al.</td>
<td>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</td>
<td>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)</td>
<td>Improved hearing in implanted ear; however, sudden, progressive SNHL on contralateral side immediately postoperatively</td>
<td>6 months</td>
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<tr>
<td>van Nierop et al.</td>
<td>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)</td>
<td>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% (&gt;48 months) Age-adjusted mean phoneme at 36 months: EVA 84%, reference group 79%, PS 91%.</td>
<td>Clear benefits in speech perceptions and QOL in PS. No difference between PS and non-PS EVA</td>
<td>12 months</td>
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<tr>
<td>Wu et al.</td>
<td>PTA (dB): 98.7</td>
<td>SRS: Consonant 88.0%, vowel 86.2%, tone 91.7%, PB word 79.2%, sentence 89.9%</td>
<td>Children with either SLC26A4 or GJB2 mutations excelled in speech perception performance after cochlear implantation</td>
<td>3.7 years</td>
</tr>
<tr>
<td>Wu et al.</td>
<td>Not reported</td>
<td>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</td>
<td>Good performance post implantation</td>
<td>3 years</td>
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<td>Wu et al.</td>
<td>CI before 3.5 years (n=6): CAP 2, SIR 1, CI after 3.5 years (n=17): CAP 4, SIR 3</td>
<td>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.</td>
<td>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</td>
<td>5 years</td>
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</tbody>
</table>
Table 2. Summary of audiological outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Preoperative data</th>
<th>Postoperative data</th>
<th>Overall benefit (subjective assessment)</th>
<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>Yamazaki et al.</td>
<td>ABR: No response bilaterally at 105 dB</td>
<td>Japanese infant word discrimination test: 90% Descriptive outcomes: Patient understood conversation without lip-reading with a familiar talker at 14 months postimplant. No developmental delay</td>
<td>Good hearing outcomes post implantation</td>
<td>5 years</td>
</tr>
<tr>
<td>Yan et al.</td>
<td>PTA (dB): 98.4±4.62, MAIS (Meaningful Auditory Integration Scale): 4, CAP: 1.5, SIR: 0.25</td>
<td>PTA (dB): Not reported, MAIS: 28 at 12 months, 31 at 24 months, CAP: 6 at 12 months, 6.8 at 24 months, SIR: 2.4 at 12 months, 3.1 at 24 months</td>
<td>Patients with SLC26A4-related deafness clearly benefit from CI</td>
<td>24 months</td>
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</table>

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 audiology (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 post-implantation. 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 method 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 [30]. 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, predominantly 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 [27,32,40], 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 auditory 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 [22,40].
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 auditory 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. showed patients with Pendred syndrome to have comparable audiological performance after CI compared with other patients with a genetic hearing loss; however, 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. Several studies demonstrated children possessing SLC26A4 mutations to have better outcomes than those with genetically undiagnosed hearing loss. 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. Consequently, candidates who can expect excellent outcomes from CI may be identified by isolating those with syndromes that exclusively affect the inner ear. The value of genetically screening the patients before implantation was emphasized in many studies.

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 patients receiving their CI before the age of 3.5 years. Furthermore, Govaerts et al. 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.

In patients experiencing a fluctuant pattern of hearing loss, the decision 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 improvement exists. Sweetow et al. 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 concluded that cochlear implantation should not be delayed in children with fluctuating hearing loss owing to the effect on speech and language development. In fact, it has been argued that the fluctuating pattern of hearing loss is in itself an indication to avoid delay. Ko et al. 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 intelligibility 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. Ko et al. 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 intelligibility and perception tools.

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CONCLUSION

Hearing outcomes after CI in Pendred syndrome are generally good with the majority of patients experiencing a benefit in terms of both hearing 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.
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 the 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
2. Pendred V. Deaf-Mutism and Goitre. The Lancet 1896; 148: 532. [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]
32. Demir B, Cesur S, Incáz S, Alberalard N, 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]
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]  
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]  
42. Govaerts PJ, De Beukelaer C, Daemers K, De Ceulaer G, Yperman M, Somers T, et al. Outcome of cochlear implantation at different ages from 0 to 6 years. Otol Neurotol 2022; 23: 885-90. [Crossref]  
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]  
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]  
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]  