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Review

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

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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 bialleleic (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.

MAIN POINTS

- Hearing outcomes following cochlear implantation in Pendred Syndrome are generally good.
- The main operative risk is of CSF leak intraoperatively, however major complications are rare.
- Due to the variability of presentation clinical judgement should be used to identify the optimum time for implantation.

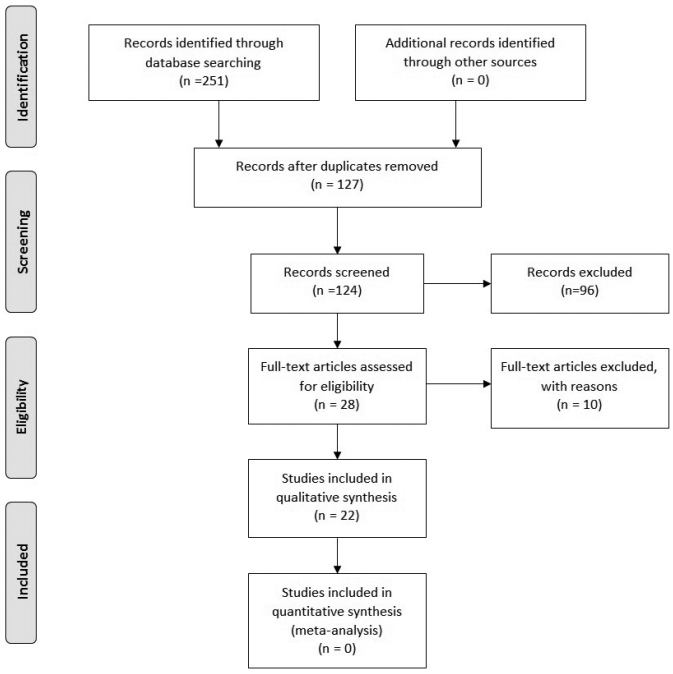

Figure 1. PRISMA Flowsheet showing study identification process

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. [36]	2013	UK	7	Children	Retrospective case series	IV
Chiong et al. [25]	2018	Philippines	4	Adults and children	Retrospective case series	IV
De Wolf et al. [37]	2010	Netherlands	2	Children	Retrospective case series	IV
Demir et al. [32]	2019	Turkey	18	Adults and children	Retrospective case-control	IV
Fahy et al. [33]	2001	UK	4	Children	Retrospective case series	IV
Gratacap et al. [30]	2015	France	14	Children	Retrospective case series	IV
Ko et al. [40]	2013	Taiwan	42	Adults and children	Retrospective case-control	IV
Kontorinis et al. [20]	2011	Germany	5	Adults and children	Retrospective case series	IV
Kuthubutheen et al. [19]	2012	Australia	1	Child	Prospective case report	IV
Loundon et al. [34]	2005	France	11	Children	Retrospective cohort study	III
Mikkelsen et al. [38]	2019	Denmark	1	Child	Retrospective case report	IV
Park et al. [24]	2017	Korea	9	Children	Retrospective case series	IV
Roh et al. [26]	2017	Korea	8	Children	Retrospective case series	IV
Steinbach et al. [29]	2006	Germany	1	Adult	Retrospective case report	IV
Sweetow et al. [22]	2005	USA	1	Child	Retrospective case report	IV
Vaisbuch et al. [35]	2019	USA	1	Adult	Retrospective case report	IV
van Nierop et al. [39]	2016	Netherlands	28	Adults and children	Retrospective cohort study	III
Wu et al. [28]	2008	Taiwan	18	Children	Prospective cohort study	III
Wu et al. [21]	2011	Taiwan	22	Children	Prospective cohort study	III
Wu et al. [27]	2015	Taiwan	23	Children	Prospective cohort study	III
Yamazaki et al. [31]	2014	Japan	1	Child	Retrospective case report	IV
Yan et al. [13]	2013	China	10	Children	Retrospective case series	IV

*Oxford Centre for Evidence-Based Medicine

Table 2. Summary of audiological outcomes

Study	Preoperative data	Postoperative data	Overall benefit (subjective assessment)	Follow-up
Broomfield et al. [36]	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. [25]	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. [37]	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. [32]	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). Improvements in all parameters from pre- to post operation were statistically significant	Patients with LVAS benefit from CI	x
Fahy et al. [33]	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: 4, 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 ildren, especially at chhigher frequency ranges	12 months
Gratacap et al. [30]	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 (Continued)

Study	Preoperative data	Postoperative data	Overall benefit (subjective assessment)	Follow-up
	Speech perception scores: Aided OSW mean 50, median 55 (0–100).			
Ko et al. [40]	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: 76.8.2±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. [20]	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)	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%.		

Table 2. Summary of audiological outcomes (Continued)

Study	Preoperative data	Postoperative data	Overall benefit (subjective assessment)	Follow-up
			Patients with PS are good candidates for CI	4.8 years
Kuthubutheen et al. [19]	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 kHz	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. [34]	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=0), non-grammatical sentences (n=2), no speech (n=1).	Good outcomes in perception and linguistics	24 months
Mikkelsen et al. [38]	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. [24]	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), 5.0 (0.0), 5.5 (0.5). Subgroup 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. [26]	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+/-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 (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 electroacoustic stimulation in speech understanding in both quiet and noisy conditions	18 months

Table 2. Summary of audiological outcomes (Continued)

Study	Preoperative data	Postoperative data	Overall benefit (subjective assessment)	Follow-up
Steinbach et al. [29]	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. [22]	Word recognition testing (WRT): Age 5: 60% R, 78% L (NU-CHIPS stimuli), aided 68% (WIPI stimuli) Age 10: 40% R, 52% L (PBK-50 stimuli), aided R 64%, aided L 68% (WIPI 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. [35]	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. [39]	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 (adults) 36 months (children)	12 months
Wu et al. [28]	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. [21]	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. [27]	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

Table 2. Summary of audiological outcomes (Continued)

Study	Preoperative data	Postoperative data	Overall benefit (subjective assessment)	Follow-up
Yamazaki et al. [31]	ABR: No response bilaterally at 105 dB	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	Good hearing outcomes post implantation	5 years
Yan et al. [13]	PTA (dB):98.4±4.62 MAIS (Meaningful Auditory Integration Scale): 4 CAP: 1.5 SIR: 0.25	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	Patients with SLC26A4-related deafness clearly benefit from CI	24 months

ABR: Auditory brainstem response; BKB: Bench–Kowal–Bamford sentences; CAP: Categorical auditory performance test; CI: Cochlear implant; FDA-Test: Frenchay Dysarthria Assessment; FMT: Freiburg monosyllable testing; HSM: Hochmair-Schulz-Moser sentence test; IT-MAIS: Infant-toddler meaningful auditory integration scale; LiP: Listening progress profile; LVAS: Large vestibular aqueduct syndrome; NCIQ: Nijmegen cochlear implant questionnaire; OSW: Open-set monosyllabic word; PBK: Phonetically balanced kindergarten test; PEACH: Parents' evaluation of aural/oral performance of children; PPVT: Peabody picture vocabulary test; PROM: Patient-reported outcome measures; PS: Pendred syndrome; PTA: Pure-tone audiometry; SIR: Speech intelligibility ratings; SNHL: Sensorineural hearing loss; SNR: Signal-to-noise ratio; WDS: Word discrimination score.

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 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 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 [35]. 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 [32,40].

Van Nierop et al. considered that patients with confirmed Pendred syndrome and those with nonsydromic 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.,[42] 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.[36] 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 [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 exclusively affect the inner ear. The value of genetically screening the patients before implantation was emphasized in many studies [6,24,28,33,36].

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 patients 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 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 [40]. 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 concluded that cochlear implantation should not be delayed in children with fluctuating hearing loss owing to the effect on speech and language development [30,38]. In fact, it has been argued that the fluctuating pattern of hearing loss is in itself an indication to avoid delay [44]. Ko et al.[40] 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 [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 implantation has been emphasized by several authors, particularly alongside genetic testing [27,31,37,38]. 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 nonsyndromic EVA to present with an air-bone gap without any middle-ear pathology. The precise mechanism is not fully understood; however, 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 [48]. The most common complication described in the literature is the CSF "gusher," a term describing the egress of clear fluid upon cochleostomy [49]. The terminology 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 perilymph gusher can be considered a misnomer [50]. Furthermore, Papsin[41] argued that only pulsatile leaks of CSF for over 1 min should be classified as "gushers," suggesting that there may be an overestimation 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 patients, with no reports of meningitis. Auditory outcomes were not described in relation to CSF gusher in the included studies; however, Adunka 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; therefore, 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 [15,54] 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 because 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 insertion, causing changes in the intracranial CSF volume. A recommendation 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 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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