Cochlear Implantation Outcomes in Post Synaptic Auditory Neuropathies: A Systematic Review and Narrative Synthesis

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To establish outcomes following cochlear implantation (CI) in patients with postsynaptic auditory neuropathy (AN). 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 98 studies in total, of which 14 met the inclusion criteria reporting outcomes in 25 patients with at least 28 CIs. Of these, 4 studies focused on Charcot-Marie-Tooth disease (CMT), 3 on Brown-Vialetto-Van-Laere syndrome (BVVL), 2 on Friedreich Ataxia (FRDA), 2 on Syndromic dominant optic atrophy (DOA+), 2 on Cerebellar ataxia - areflexia - pes cavus - optic atrophy - sensorineural hearing loss (CAPOS) syndrome, and 1 on Deafness-dystonia-optic neuronopathy (DDON) syndrome. All studies were Oxford Centre for Evidence Based Medicine (OCEBM) grade IV. Overall trend was towards good post-CI outcomes with 22 of the total 25 patients displaying modest to significant benefit. Hearing outcomes following CI in postsynaptic ANs are variable but generally good with patients showing improvements in hearing thresholds and speech perception. In the future, development of a clearer stratification system into pre, post, and central AN would have clinical and academic benefits. Further research is required to understand AN pathophysiology and develop better diagnostic tools for more accurate identification of lesion sites. Multicenter longitudinal studies with standardized comprehensive outcome measures including health-related quality of life data will be key in establishing a better understanding of short and long-term post-CI outcomes.

KEYWORDS: Cochlear Implants, Cochlear Nerve, Hearing Loss, Systematic Review

INTRODUCTION

Background and Epidemiology

Auditory neuropathy (AN) is a term, first coined in 1996 by Starr et al.[1], that describes a pattern of hearing loss in which there is altered function of the auditory nerve with functional preservation of the outer hair cells of the cochlea. Defective functioning of the auditory nerve is characterized by absent or severely abnormal auditory brainstem responses, although the preservation of the cochlea and its outer hair cells is indicated by normal evoked otoacoustic emissions and/or cochlear microphonics[2]. The other characteristic feature of hearing loss in patients with AN is significant impairment of speech discrimination abilities relative to pure-tone thresholds. The underlying mechanism is hypothesized to be a result of deficits in coding of temporal neural cues, critical for sound localization, speech perception, and signal identification in the presence of background noise[3].

Although AN can occur in all age groups, there is uncertainty regarding its prevalence. Estimations of AN related hearing loss range between 1% and 10% of all individuals with hearing loss[4,5]. This significant variation in prevalence may be attributed to the wide range of ANs described by these studies. Exacerbating this uncertainty is the complexity of diagnosing AN, which often requires a number of specialist audiological and genetic tests. Consequently, prevalence might be underestimated due to omission of hearing disorders that have not been fully described and labeled.

The first two author contributed equally to this work.
Classification of ANs
The clinical profile of ANs is heterogeneous, encompassing of a wide range of acquired, genetic (syndromic/non-syndromic), and congenital etiologies. Risk factors are also diverse, including perinatal and neonatal factors, such as hypoxia, hyperbilirubinemia, ototoxic drug exposure, and infections such as meningitis. To date, multiple synonymous terms have been coined for a more appropriate classification, the main ones being auditory dyssynchrony and auditory neuropathy spectrum disorder (ANSD), with the latter term being preferred as it helps mitigate some of the heterogeneity by grouping together these similar, yet distinct, conditions. However, as noted by Rance et al. in 2015, the term is becoming redundant as ‘spectrum disorder’ denotes conditions where objective measures are lacking, and this is not the case here, given the recent advancements in the field of AN.

Using audiological and electrophysiological measures, AN can be broadly classified by the anatomical locus of dysfunction. These divisions include presynaptic disorders, postsynaptic disorders, and central neural pathway disorders. In presynaptic ANs, such as otoferlin mutations, the site of lesion is the inner hair cells or ribbon synapses. The proposed pathophysiology is a combination of reduction in the volume of glutamate and increased latency period in its release at the ribbon synapses, ultimately resulting in disruption of temporal coding. In postsynaptic ANs, dysfunction can occur at multiple sites along the auditory nerve pathway, including unmyelinated auditory nerve dendrites or auditory ganglion cells and their myelinated axons and dendrites. Here, the pathophysiology varies on the basis of the nature of the etiology, whether it is demyelination, axonal degeneration, or a combination of both. Demyelination slows conduction velocity causing dyssynchrony and axonal degeneration resulting in reduced auditory input to the brainstem. Finally, in central ANs, the site of lesion is located at the brainstem level, including cerebellar-lo-pontine angle tumors, such as vestibular schwannomas and meningiomas. Figure 1 demonstrates a schematic representation of these divisions.

Syndromic dominant optic atrophy (DOA+)
The Optic Atrophy 1 (OPA1) gene codes for the mitochondrial dynamin related GTPase protein, which is crucial for mitochondrial function and stability. Mutations in the OPA1 gene causes dominant optic atrophy (DOA) or syndromic dominant optic atrophy (DOA+), which is characterized by optic atrophy as well as AN with published data on cochlear implant outcomes are included in this systematic review. These are described below, and the summary of all 11 conditions is presented in Table 1.

Deafness-dystonia-optic neuropathy (DDON) syndrome
Deafness-dystonia-optic neuropathy (DDON) syndrome also known as Mohr-Tranebjaerg syndrome is a recessive X-linked progressive neurodegenerative syndrome caused by a mutation in the TIMM8A gene. This gene encodes for the protein translocase of the mitochondrial inner membrane 8A, which is responsible for the transfer of metabolites from the cytoplasm into the mitochondrial inner membrane. The pathophysiology of this syndrome is characterized by progressive degeneration of the terminal axons of the spiral ganglion neurons.

MAIN POINTS

- This review was only able to identify studies relating to 6 of the 11 postsynaptic AN pathologies identified in the scoping searches: CMT, BVVL, FRDA, DOA+, CAPOS, and DDON syndrome.
- Hearing outcomes across aetiologies were generally good, with 88% (22/25) of patients showing modest to significant benefit post-CI.
- The methodological quality of included studies was poor, consisting of case reports and small volume case series. All studies were OCEBM grade IV. One study contributed 32% (8/25) of all patients included in this review.
- Further research is required to understand AN pathophysiology and develop better diagnostic tools (audiological and genetic) for more accurate identification of lesion sites.
- Multicentre longitudinal studies with standardised comprehensive outcome measures including through health-related quality of life data will be key in establishing a better understanding of short and long-term post-CI outcomes.

Figure 1. Overview of the peripheral auditory system showing the presynaptic, postsynaptic, and central sites of lesions associated with auditory neuropathy. Illustration inspired by Moser et al. 2016.
Patients present with early childhood onset AN, adolescent dystonia and ataxia, and decreased visual acuity in the third decade followed by dementia in their fourth

Brown-Vialetto-Van-Laere syndrome (BVVL) Brown-Vialetto-Van-Laere (BVVL) syndrome is a rare progressive neurodegenerative disorder which is thought to be caused by mutations in the SLC52A3, SCL52A2, or SCL52A1 genes, which encode the interstitial riboflavin transporters hRFT3, hRFT2, and hRFT1

Cerebellar ataxia - areflexia - pes cavus - optic atrophy - sensorineural hearing loss (CAPOS syndrome)

This table has been produced with the aid of tables from Shearer et al., 2019 and Santarelli et al., 2010.

Table 1. Summary table of postsynaptic auditory neuropathies and their phenotypes

| Name of condition/syndrome | Gene | Phenotype | References |
|-----------------------------|------|-----------|------------|
| Syndromic dominant optic atrophy (DOA+) | OPA1 | Optic atrophy as well as auditory neuropathy presenting with moderate to severe hearing loss | (44) |
| Deafness-dystonia-optic neuronopathy (DDON) syndrome | TIMM8A | Childhood onset auditory neuropathy; slowly progressive dystonia and ataxia in teens; decreased visual acuity at approximately age 20; dementia at approximately 40 years of age | (12) |
| Brown-Vialetto-Van-Laere syndrome (BVVL) | SLC52A3; SCL52A2; SCL52A1 | Progressive pontobulbar palsy; sensorineural deafness; facial weakness; respiratory compromise | (13,15) |
| Cerebellar ataxia - areflexia - pes cavus - optic atrophy - sensorineural hearing loss (CAPOS syndrome) | ATP1A3 | Slowly progressive sensorineural hearing loss; optic atrophy; acute episodes of neurological deterioration; ataxia; areflexia | (16) |
| Charcot-Marie-Tooth disease (CMT) | PM22 (CMT 1A); MPZ (CMT 1B) | Mild to severe deafness; demyelinating neuropathy | (17)(45) |
| Friedreich's ataxia (FRDA) | FXN | Ataxia; optic neuropathy; axonal neuropathy; normal hearing threshold; hypertrophic cardiomyopathy; mild deafness | (18) |
| Leber Hereditary Optic Neuropathy (LHON) | 95% of LHON cases are primarily one of the three mtDNA point mutations: G3460A, G11778A, and T14484C, | Characterized by bilateral subacute loss of central vision due to focal degeneration of the retinal ganglion cell layer and optic nerve; mild-moderate deafness | (46,47) |
| Autosomal dominant NSHL | DIAPH3 | The DIAPH3 gene encodes for the diaphanous formin 3 protein. This category of proteins is involved in maintenance of cell polarity and cell shape, intracellular transport, and vesicular trafficking. Localization of DIAPH3 within the inner ear and function in cochlea are not yet certain. In affected patients moderate to profound deafness has been observed | (48,49) |
| Common cavity malformation and auditory neuropathy autosomal recessive | ROR1 | ROR1 gene encodes for tyrosine kinase-like receptor-1 which is a transmembrane protein localized at the plasma membrane. ROR1 to be crucial for spiral ganglion neurons to innervate auditory hair cells. ROR1 mutation have been found in a family with autosomal recessive deafness associated with a common cavity inner ear malformation | (50) |
| X-linked auditory neuropathy and Cowchock Syndrome | AIFM1 | Variants in AIFM1 gene are a common cause of familial and sporadic ANSD. There is a lot of phenotypical variation, but common features of these disorders are developmental disabilities such as mental retardation, motor dysfunction and muscle weakness | (51) |
| Autosomal recessive NSHL; Leigh syndrome (progressive neurodegenerative disease) | NARS2 | NARS2 encodes for the mitochondrial asparagine-tRNA ligase protein involved in spiral ganglion energy metabolism. Individuals with mutation in this gene showed absent ABRs, present CM, and absent OAEs by week 11 | (52) |

These transporters are responsible for the cellular uptake of riboflavin, which is an essential component in oxidative metabolism and functional maintenance of the neurons. BVVL is characterized by progressive pontobulbar palsy associated sensorineural deafness, facial weakness, and respiratory compromise.

Cerebellar ataxia - areflexia - pes cavus - optic atrophy - sensorineural hearing loss (CAPOS syndrome) Cerebellar ataxia - areflexia - pes cavus - optic atrophy - sensori-
neural hearing loss (CAPOS) syndrome is caused by mutations in the ATP1A3 gene which encodes for the catalytic α3-subunit of the transmembrane Na+/K+ ATPase (NKA) pump\textsuperscript{10}. The NKAα3 plays a crucial role in the regulation of electrochemical gradients across the plasma membrane\textsuperscript{16}. Disruption leads to the inability of the neuron to establish its resting membrane potential after excitatory activity. Affected individuals typically present with slowly progressive sensorineural hearing loss, optic atrophy, acute episodes of neurological deterioration, as well as accompanying ataxia and areflexia\textsuperscript{11}. 

Charcot-Marie-Tooth disease (CMT) 
Charcot-Marie-Tooth disease (CMT) is a heterogenous group of inherited sensorimotor neuropathies (HSMN). Its clinical profile presents as progressive motor and sensory neuropathy with variable severity and inheritance patterns. To date, more than 80 genes have been associated with CMT; however, the 2 genes particularly associated with CMT involving auditory neuropathy are MPZ (CMT 1A) and PMP22 (CMT 1B)\textsuperscript{10,17}.

Friedreich Ataxia (FRDA) 
Friedreich Ataxia (FRDA) is the most common of the autosomal recessive ataxias accounting for approximately 25% of all autosomal recessive cerebellar ataxias\textsuperscript{18}. FRDA is caused by mutations in the FXN gene with 98% of mutant alleles have a GAA trinucleotide repeat expansion in intron 1 of the gene. It is characterized by progressive limb and trunk ataxia, hypertrophic cardiomyopathy, and scoliosis\textsuperscript{19}. Hearing loss in FRDA is one of the less common presenting symptoms and is believed to have a similar site of lesion as CMT with damage at the level of the spiral ganglion neuron\textsuperscript{11}. 

Cochlear implantation (CI) in postsynaptic AN 
In patients with AN, conventional hearing aids offer limited benefit as these devices primarily provide auditory amplification and are unable to correct for neural dyssynchrony\textsuperscript{20}. In contrast, cochlear implants are a useful rehabilitative tool and are considered the treatment modality of choice for ANs. CI bypasses the sensory and synaptic partitions and directly stimulates the spiral ganglion somata, resulting in direct transmission of electrical signals to the midbrain\textsuperscript{10,21}. Direct nerve stimulation improves neural synchrony, aiding speech comprehension and allowing development of critical speech and hearing skills.

Although CI outcomes in patients with AN are variable, the majority of patients seem to benefit with improvements across their speech perception, language development, and communication. The observed efficacy of CI seems to be closely related to the locus of the lesion. In presynaptic ANs, outcomes are invariably good with follow-up audiological results similar to patients with cochlear type sensorineural hearing loss\textsuperscript{21,22}. CI outcomes in postsynaptic AN have been reported as much more variable. This is partially explained by the wide array of etiologies classified as postsynaptic ANs, compounded by their relative rarity and limited published data.

Objectives 
The aim of this review was to collect and synthesize available literature on CI outcomes in patients with postsynaptic ANs. Pooling this data may lead to more reliable estimations of cochlear implant efficacy on the basis of the etiology of the AN and subsequently enable improved patient counseling and management. 
Population: Children or adults with postsynaptic ANs 
Intervention: CI (with or without auditory training, rehabilitation, or acoustic hearing aids) 
Comparison: No comparison group 
Outcomes: Primary outcomes were preimplantation versus. post-implantation audiomentric outcomes (for example, pure-tone audiometry and/or speech perception scales). Where preimplantation outcomes were not available, only postimplantation audiometric outcomes were noted. Secondary outcomes included intraoperative and postoperative adverse events, use of cochlear implant at follow-up, and patient reported outcome measures (PROMs), such as quality of life scores.

MATERIALS AND METHODS 
The study protocol was registered in the PROSPERO prospective database of systematic reviews (187370- awaiting confirmation).

Study Inclusion Criteria 
Eligibility criteria for inclusion were clinical studies of CI in patients of any age with a clinical or genetic diagnosis of postsynaptic AN and at least one form of audiometric postimplantation outcome data. Exclusion criteria were patients with a diagnosis of ANSD without clarification of etiology or site of lesion. Studies without postoperative audiometric outcomes or inaccessible full texts were also excluded. With the exception of animal and pharmacological model studies, no exclusion criteria were applied to study design with all experimental and observational designs included. These broad inclusion criteria allowed a more comprehensive perspective to be established given the limited literature available that was found during scoping searches.

Search Strategy 
In total, 2 reviewers (DC/AC) independently performed the searches of the following databases: MEDLINE, Ovid EMBASE, Web of Science, Cochrane Collection, ClinicalTrials.gov. A full list of the search terms used for MEDLINE is shown in Appendix A. These terms were also used to search the remaining literature archives with only minor adjustments to account for database-specific search terms. No limits were placed on language or year of publication.

Selection of Studies 
A total of 2 reviewers (DC/AC) independently screened all the records retrieved from the databases for relevancy first by title, then by abstract, and finally by full-text review for eligible studies. Any disagreements were resolved through consultation with a third reviewer (JM). Studies without accessible abstracts, full text, or missing data were followed up by contacting The British Library along with the primary authors of the study. If these steps failed to yield results, they were excluded. Where studies presented overlapping populations, the study with the larger population set was chosen after ensuring no additional data points were being lost. After a full-text analysis, reference lists of all eligible publications were screened independently by the 2 reviewers (DC/AC) to identify any additional trials or studies.

Data Extraction 
Data were extracted by the first reviewer (DC) and then checked by the second reviewer (AC). Extracted data was arranged in a spread-
Risk of Biased Quality Scoring

Study quality and risk of biased assessment was carried out independently by 2 reviewers (DC/AC) using the Brazelli risk of bias tool for nonrandomized studies[21]. This instrument was designed to specifically assess nonrandomized studies (comparative and cohort studies) and has also been adapted for use in case series. In addition, the levels of evidence were graded according to the Oxford Centre for Evidence Based Medicine grading system (OCEBM)[22]. Any discrepancies between the reviewers were resolved by discussion.

RESULTS

Searches were initially run on the March 23, 2020 and yielded a total of 147 results. After removal of duplicates, the total number of studies remaining was 98. These then underwent title, abstract, and full-text screening giving a total of 13 studies. Finally, hand searching the bibliographies of these 13 papers and various journals, an additional study was identified bringing the total number of eligible studies to 14. A flowsheet detailing study selection according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines is included in Figure 2.

Description of Studies

In total, 14 studies finally met the inclusion criteria, describing 25 patients who underwent 28 CI procedures (3 bilateral, 9 right sided, 8 left sided, and 5 not clarified). There were 7 single case reports and 7 cases series, of which 2 case series only had a single patient eligible for this review[23,24]. Of the 14 studies, 4 focused on CMT, 3 on BVVL, 2 on FRDA, 2 on DOA+, 2 on CAPOS syndrome, and 1 on DDON syndrome. All the studies were published between 1999 and 2020. The studies described 16 females and 9 males and both adult and pediatric patients. The average age at the time of CI was 38.6 years with ages ranging between 4 and 70 years. Follow-up periods varied significantly, ranging between 2 and 48 months, with the majority opting for 3, 6, or 12-month intervals. All studies, except one[24], reported the type of cochlear implant used, and 9 of the studies reported a genetic analysis for the included patients[24–32]. Of those 9 studies, 2 were on CMT patients, and genetic testing was inconclusive as to the mode of inheritance[26,29]. A study on 8 DOA+ patients identified 4 of them who carried the R445H mutation[26]; however, further clarification of exactly who those 4 carriers were was not provided. Study characteristics are summarized in Table 2, and patient characteristics along with CI details are summarized in Table 3.

Quality of Studies

The methodological quality of identified studies was modest as might be expected given the rare and complex nature of postsynaptic ANs. All of the eligible studies were retrospective case series or case reports and therefore OCEBM grade IV (Table 2). Moreover, 1 study contributed 32% (8/25) of all patients included in this review[28]. Other than the study designs, the major limiting factor in the quality of these studies was missing data. A key example is data regarding the rehabilitative process with only Frewin et al.[33] reporting any protocol details of substance, and 2 other studies simply stating the use of standardized rehabilitative programs with no further clarification of what these comprised[22,27]. Given the heterogeneity and limitations of the outcome data, a meta-analysis was not possible; and therefore, a narrative synthesis of the studies is presented. Quality assessment of studies is summarized in Table 4.

Audiological Outcomes

Hearing outcomes across etiologies were generally good, with 88% (22/25) of the patients showing modest to significant benefit post CI. Across studies, reporting was heterogeneous in terms of outcome measures and follow-up duration. All studies presented some form of pre and post-CI data; however, there were inconsistencies with some measures being reported only preoperatively or postoperatively without justification of omission. Pure-tone audiometry (PTA) threshold data was presented preoperatively and postoperatively for 11 studies[23,25–30,12–35], and only preoperatively for 3 studies[24,31,36]. Of the 11 studies that reported preoperative and postoperative PTA data, Sinnathuray et al.[35] reported PTA data for only 1 of their 2 patients as extensive audiometric testing had not taken place for both. Kobayashi et al.[29] did not specify when, during the follow-up period, the PTA measurements were taken. Speech perception scores were assessed using a variety of validated and non-validated instruments, including Bench-Koval-Bamford (BKB) Sentences[26,31,33,35], Turkish matrix sentence test[41], consonant-vowel-consonant (CVC) words[23,31], City University of New York Sentences (CUNY)[26,35] phonetically balanced kindergarten (PBK) test[34], minimal pairs test (closed-set)[34], AzBio sentence test[36], consonant-nucleus-consonant (CNC) word lists[36], Central Institute for the Deaf (CID) four choice spondee test[27], categorical auditory performance (CAP) test[30], auditory speech sounds evaluation[30], DeVault common phrases test[31], Manchester junior words test[31], Glendonald auditory screening procedure (GASP) phoneme detection and imitation test[31], Korean version of CID test (K-CID)[30], and Turkish matrix sentence test[34]. Both Postelamans et al.[25] and Kobayashi et al.[29] provided speech discrimination scores; however, no details were listed regarding whether they used a standardized or...
Table 2. Summary table of postsynaptic auditory neuropathies and their phenotypes

| Study               | Year | Country   | Study Design                  | Postsynaptic Auditory neuropathy (AN) | Control Group | Number of patients | Pure-Tone Audiometry | Speech Perception | PROMS and other instruments utilized | OCEBM Grade |
|---------------------|------|-----------|-------------------------------|--------------------------------------|---------------|--------------------|----------------------|-------------------|-------------------------------------|--------------|
| Leenheer et al.     | 2008 | Belgium   | Case Series (retrospective)   | Syndromic dominant optic atrophy     | No            | 1                  | Yes                  | Yes: NVA, CVC, phoneme score | PROM: No Other: No | IV         |
| Santarelli et al.   | 2015 | Italy     | Case Series (retrospective)   | Syndromic dominant optic atrophy     | Yes           | 8                  | Yes                  | Yes: Material consisted of disyllabic words which were obtained from the protocol of patient candidacy for cochlear implantation for the Italian language(53) | PROM: No Other: No | IV         |
| Sinnathuray et al.  | 2010 | Ireland   | Case Series (retrospective)   | Brown-Vialetto-Van Laere syndrome    | Yes           | 2                  | Yes                  | Yes: BKB, CUNY test | PROM: No Other: No | IV         |
| Menezes et al.      | 2016 | Australia | Case Series (retrospective)   | Brown-Vialetto-Van Laere syndrome    | Yes           | 1                  | Yes                  | Yes: BKB sentences, Manchester Junior, CVC words, GASP phoneme detection and imitation | PROM: No Other: Yes: but not reported | IV         |
| Anderson et al.     | 2019 | England   | Case Series (retrospective)   | Brown-Vialetto-Van Laere syndrome    | Yes           | 3                  | Yes                  | Yes: CAP, ASSE       | PROM: BAPP Other: Perception of speech and language therapist, compliance using data logging system | IV         |
| Han et al.          | 2017 | South Korea | Case Series (retrospective) | CAPOS Syndrome                       | Yes           | 1                  | Yes                  | Yes: SDS, K-CID score, PB word, Spondee word | PROM: No Other: No | IV         |
| Atılgan et al.      | 2019 | Turkey    | Case Report (retrospective)   | CAPOS Syndrome                       | No            | 1                  | Yes                  | Yes: Phonetically balanced word discrimination test 14, Turkish Matrix Sentence Test | PROM: No Other: Music perception abilities assessed with T-CAMP | IV         |
| Postelmans et al.   | 2006 | Netherlands | Case Report (retrospective)   | Charcot-Marie-Tooth disease type 1A   | No            | 1                  | Yes                  | Yes: does not state which speech discrimination test was used and whether this was a standardized and validated one | PROM: No Other: No | IV         |
| Goswamy et al.      | 2012 | England   | Case Report (retrospective)   | Charcot-Marie-Tooth disease type 1A   | Yes           | 1                  | Yes                  | Yes: BKB, CUNY sentences | PROM: No Other: No | IV         |
| Anzalone et al.     | 2018 | United States of America | Case Report (retrospective) | Charcot-Marie-Tooth disease (type unclassified) | No            | 1                  | Yes                  | Yes: AzBio, CNC | PROM: No Other: No | IV         |
| Kobayashi et al.    | 2020 | Japan     | Case Series (retrospective)   | Charcot-Marie-Tooth disease (type unclassified) | No            | 2                  | Yes                  | Yes: does not state which speech discrimination test was used and whether this was a standardized and validated one | PROM: No Other: No | IV         |
### Table 2. Summary table of postsynaptic auditory neuropathies and their phenotypes (continued)

| Study                  | Year  | Country           | Study Design      | Postsynaptic Auditory neuropathy (AN) | Control Group | Number of patients | Pure-Tone Audiometry | Speech Perception | PROMS and other instruments utilized | OCEBM Grade |
|------------------------|-------|-------------------|-------------------|--------------------------------------|---------------|--------------------|----------------------|-------------------|--------------------------------------|--------------|
| Brookes et al.         | 2007  | United States of America | Case Report (retrospective) | Deafness-dystonia-optic neuropathy syndrome | No            | 1                  | Yes                  | Yes               | Yes: CID four choice spondee test, Vowel feature test | IV           |
|                        |       |                   |                   |                                      |               |                    |                      |                   | PROM: No Other: Speech-language tests—Preschool language scale-3, Minnesota child development inventory, Peabody picture vocabulary test, Goldman Fristoe, Short-long sentence repetition task, Expressive vocabulary test |             |
| Miyamoto et al.        | 1999  | United States of America | Case Report (retrospective) | Friedreich's Ataxia                   | Yes           | 1                  | Yes                  | Yes: PBK (open-set), Minimal Paris Test (closed-set) | PROM: No Other: EuroQol / NCIQ Other: Localization testing – York Crescent of Sound | IV           |
| Frewin et al.          | 2013  | England           | Case Report (retrospective) | Friedreich's Ataxia                   | No            | 1                  | Yes                  | Yes: BKB          | PROM: No Other: EuroQol / NCIQ Other: Localization testing – York Crescent of Sound | IV           |

ASSE: Auditory Speech Sounds Evaluation; BAPP: Brief Assessment of Parental Perception questionnaire; BKB: Bench-Kowal-Bamford Sentences; CAP: Categorical Auditory Performance test; CID: Central Institute for the Deaf; CNC: Consonant-Nucleus-Consonant word lists; CUNY: City University of New York Sentences; CVC: Consonant-Vowel-Consonant words; GASp: Glendonald Auditory Screening Procedure Phoneme; K-CID: Korean version of central Institute for the deaf test; NCIQ: Nijmegen Cochlear Implant Questionnaire; NVA: Nederlandse vereniging voor audiologie test; OCEBM: Oxford Centre for Evidence Based Medicine; PBK: Phonetically Balanced Kindergarten Test; PROM: Patient Reported Outcome Measures; SDS: Speech Discrimination Score; T-CAMP: Turkish version of the Clinical Assessment of Music Perception Test.

### Table 3. Patient characteristics and cochlear implantation details

| Study          | Year | Postsynaptic AN type | Number of patients (no. of implants) | Sex   | Age at which sensorineural hearing loss developed | Average age at implantation (range) | Genetic Analysis | Previous Interventions | Intervention Summary |
|----------------|------|----------------------|-------------------------------------|-------|--------------------------------------------------|-----------------------------------|------------------|------------------------|----------------------|
| Leenheer et al.| 2008 | Syndromic dominant optic atrophy | 1 (1)                              | 1 Female | Developed progressive hearing loss at the age of 17 | 46 (46)                          | NR               | NR                     | Insertion Site: Left ear Cochlear implant device: Med-El Combi 40+ Full insertion: Yes Surgical Complication: NR Rehabilitation details: Patient was enrolled in a standardized post-implant rehabilitation program. |

| Santarelli et al. | 2015 | Syndromic dominant optic atrophy | 8 (8) | 6 Females 2 Males | Pt 1 = 9 / Pt 2 = 28 / Pt 3 = 25 / Pt 4 = 13 / Pt 5 = 13 / Pt 7 = Congenital / Pt 8 = 15 / Pt 9 = 15 | 33 (5-48) | 4 subjects carried the R445H mutation, not stated which patients thought | INSERTION SITE: 6 Right Ear (PT: 1, 2, 3, 4, 5, 7, 8) 2 Left Ear (2, 9) Cochlear Implant device: 7 C124RE (PT ID: 1, 2, 3, 4, 5, 7, 8) HiRes90K (PT: ID: 9) Full insertion: NR Surgical Complication: NR Rehabilitation details: NR |
| Study            | Year | Postsynaptic AN type | Number of patients (no. of implants) | Sex | Age at which sensorineural hearing loss developed | Average age at implantation (range) | Genetic Analysis | Previous Interventions | Intervention Summary |
|------------------|------|----------------------|--------------------------------------|-----|-------------------------------------------------|----------------------------------|-----------------|------------------------|----------------------|
| Sinnathuray et al. | 2010 | Brown-Vialetto-Van Laere syndrome | 2 (2) | 1 Female 1 Male | Patient 1 developed progressive hearing loss ~ 9 years of age. Patient 2 suffered from hearing problems from age 14.5 | 43 (41-45) | NR | Patient 1 – Bilateral High-powered HA since age 14 – very limited benefit. Patient 2 intermittently used HA due to background noise amplification | Insertion Site: Left ear (for both pts.) Cochlear implant device: Pt. 1: Nucleus 24 contour device; Patient 2: Nucleus Freedom with contour advance device. Surgical Complication: Pt. 1: On extubation, the patient suffered a prolonged apneic episode and required reintubation and transfer to intensive care unit for 24 hours. He made a satisfactory recovery and was discharged 3 days postoperatively; No surgical complications were reported in pt. 2. Rehabilitation details: NR |
| Van Laere | 2016 | Brown-Vialetto-Van Laere syndrome | 1 (1) | 1 Female | Hearing loss began at age 9 | 10.5 (10.5) | p.G306R mutation in SLC52A2 | 1.) HA – no benefit 2.) High dose riboflavin treatment for 12 months after diagnosis | Insertion Site: Left ear Cochlear implant device: Nucleus CI422 Full insertion: NR Surgical Complication: NR Rehabilitation details: NR |
| Anderson et al. | 2019 | Brown-Vialetto-Van Laere syndrome | 3 (3) | 2 Females 1 Male | Patient 1 – Age at onset of hearing loss was 2.0, age at diagnosis was 5.0. Patient 2 – Age at onset of hearing loss was 1.5, age at diagnosis was 2.0. Patient 3 – Age at onset of hearing loss was 5.0, age at diagnosis was 5.1 | 7.9 (6.9-8.9) | Pt 1 (RFVT3 deficiency due to SCL52A2 mutation) Pt 2 (RVFT2 deficiency due to SLC52A3 mutation) Pt 3 (RVFT3 deficiency due to SCL52A2 mutation) | Pt 1: Riboflavin treatment at age 5 initiated (40 0mg 3x day). Led to significant improvement in general symptoms (mobility, swallowing and breathing) but there was no reported benefit in her hearing. Pt 2: Riboflavin HA – were also trialed HA but pt. received no benefit. Pt 2: Riboflavin Treatment – commenced within 6 months of the onset of her hearing loss. As a result of this patient showed an improvement in general symptoms | Insertion Site: All three unilateral (NR which ear) Cochlear implant device: C1522 and Cochlear CP910 processor for all three Full insertion: NR Surgical Complication: NR Rehabilitation details: NR |
| Study    | Year | Postsynaptic AN type | Number of patients (no. of implants) | Sex | Age at which sensorineural hearing loss developed | Average age at implantation (range) | Genetic Analysis | Previous Interventions | Intervention Summary |
|---------|------|-----------------------|--------------------------------------|-----|-----------------------------------------------|-----------------------------------|-----------------|------------------------|----------------------|
| Han et al. | 2017 | CAPOS Syndrome | 1 (1) | 1 Female | Hearing loss began in her teenage years | 24 (24) | WES identified de novo occurrence of an autosomal variant p.E818K of the ATP1A3 gene located on chromosome 19q13.2 | Hearing aids were trialed but made her speech discrimination worse due to the amplification of background noises | Insertion Site: NR Cochlear implant device: NR Full insertion: NR Surgical Complication: NR Rehabilitation details: NR |
| Atılgan et al. | 2019 | CAPOS Syndrome | 1 (1) | 1 Female | Patient suffered from varicella disease when she was 8-year old. Hearing loss occurred after this febrile illness | 12 (12) | Pt. carried a heterogeneous variant, c.2491 G>A: p.E831K of the ATP1A3 gene | Patient briefly used a bilateral hearing aid equipped with frequency modulation system at age 11. However, she rejected the device after complaints of poor speech perception abilities | Insertion Site: Right ear Cochlear implant device: Nucleus CI24RE Full insertion: NR Surgical Complication: NR Rehabilitation details: NR |
| Postelmans et al. | 2006 | Charcot-Marie-Tooth disease type 1A | 1 (1) | 1 Female | Developed progressive bilateral hearing loss since ~ 8 yrs | 53 (53) | Genetic analysis showed a substitution (G >T exchange) at nucleotide 193 in exon | | |
| Study | Year | Postsynaptic AN type | Number of patients (no. of implants) | Age at which sensorineural hearing loss developed | Average age at implantation (range) | Genetic Analysis | Previous Interventions | Intervention Summary |
|-------|------|----------------------|--------------------------------------|-----------------------------------------------|----------------------------------|-----------------|----------------------|----------------------|
| Goswamy et al. | 2012 | Charcot-Marie-Tooth disease type 1A | 1 (1) | Male | Patient considered himself to be deaf from early in his first decade | 67 (67) | Genetic testing was inconclusive as to the mode of inheritance | Hearing Aids for 15 years but no reported benefit | Insertion Site: Left ear Cochlear implant model: Med-El FlexSOFT Full insertion: Yes Surgical Complication: No postoperative complications occurred Rehabilitation details: NR |
| Anzalone et al. | 2019 | Charcot-Marie-Tooth disease (type unclassified) | 1 (1) | Male | Reported a 15-year duration of deafness involving the left ear | 70 (70) | NR | Bilateral hearing aid user but subsequently stopped using his hearing aid in the left ear several years prior to presentation due to experiencing progressive audiometric decline | Insertion Site: Left ear Cochlear implant model: MED-EL™ Synchrony Flex® 28 Full insertion: Yes Surgical Complication: NR Rehabilitation details: NR |
| Kobayashi et al. | 2020 | Charcot-Marie-Tooth disease (type unclassified) | 2 (4) | Male | Patient 1 – progressive bilateral hearing loss began from age 10. Patient 2 was referred for progressive SNHL since 6 years of age | 19.5 (16-23) | Y – genetic test for congenital hearing loss about the presence of 154 mutations in 19 genes reported as a cause of hearing loss was negative | NR | Insertion Site: Pt. 1: Bilateral (sequential, left ear first and 18 months later right ear); Pt 2: Bilateral (simultaneous) Cochlear implant model: Pt. 1: Flex 28 Concerto® in R and; Pt. 2: CI522 in R and L Full insertion: Yes Surgical Complication: NR Rehabilitation details: NR |
| Brookes et al. | 2007 | Deafness-dystonia-optic neuronopathy syndrome | 1 (1) | Male | Receptive and expressive language delay was diagnosed after age 2. AN was diagnosed at age 3.5 | 4 (4) | Y – Genetic testing at age 5 identified a deletion ~6 kbp that included axons 17-19 of BTK and exon 1 of DDP1/TIMM8a | Hearing aid trial began at age 3.5. This trial improved hearing to a mild-moderate loss for both pure tones and speech perception. However, hearing loss progressed | |
### Table 3. Patient characteristics and cochlear implantation details (continued)

| Study       | Year | Postsynaptic AN type | Number of patients (no. of implants) | Sex | Age at which sensorineural hearing loss developed | Average age at implantation (range) | Genetic Analysis | Previous Interventions | Intervention Summary |
|-------------|------|----------------------|-------------------------------------|-----|-----------------------------------------------|----------------------------------|------------------|-----------------------|----------------------|
| Miyamoto et al. | 1999 | Friedreich's Ataxia | 1 (1)                               | Male | 10.9 (10.9)                                  | NR                               | At age 5 a loaner hearing aid was fit for the right ear and 20 dB functional gain was noted initially. By 1 month no further improvement was seen. | Insertion Site: Right ear<br>Cochlear implant device: Nucleus 22<br>Full insertion: NR<br>Surgical Complication: NR<br>Rehabilitation details: NR |
| Frewin et al. | 2013 | Friedreich's Ataxia | 1 (2)                               | Female | Diagnosed with FRDA at age 10, age at hearing loss not reported | 41 (41)                           | Hearing Aid were trialed | Insertion Site: Bilateral<br>(sequential, right side first and then left side 8 months afterwards)<br>Cochlear implant model: Right side = Nucleus CI512; Left side = Nucleus Freedom Contour<br>Advance implant Full insertion: Yes<br>Surgical Complication: No postoperative complications occurred<br>Rehabilitation details: A predominately home-based program was utilized, comprising of audiobooks, and auditory training material for family members to complete with the patient. Regular appointments were made to informally monitor progress and consolidating equipment skills. |
validated instrument. Santarelli et al.\textsuperscript{[28]} study was the only one that utilized statistical analysis. They reported that all DOA+ patients who underwent CI had significant improvement in their mean disyllable recognition scores 1-year post CI in a quiet environment and in the presence of background noise, except for subject 9 (paired t-test, \(p<0.01\)).

Out of the 14 studies, only 3 had control groups\textsuperscript{[26,28,34]}: Goswamy et al.\textsuperscript{[26]} compared the speech discrimination scores of their single patient with CMT with those of an average of all patients who had CI testing between 2008 and 2009 in the Manchester cochlear implantation program (\(n=44\)) and found his progress to be slower; however, by 9 months, his open-set discrimination had significantly improved, and his CUNY test percentage was 13\% higher than the control. Miyamoto et al.\textsuperscript{[34]} had a control group comprising of 7 children who had experienced progressive sensorineural hearing loss and had Nucleus 22-channel cochlear implants. Their single patient with FRDA demonstrated improvement in the closed-set vowel recognition on the minimal pairs test (82\% correct) by 1 year after implantation, which was only slightly lower than that of the control group (92\%).

However, his consonant recognition and open-set word recognition (PBK test) were comparatively much lower. Finally, Santarelli et al.\textsuperscript{[28]} presented the mean PTA data for 583 ears with cochlear hearing loss (range 18–50 years) for comparison to their DOA+ cohort. They reported lower scores in patients with DOA+ versus the hearing-impaired controls for all PTA classes.

The studies also employed a range of other outcome measures to assess expressive and receptive language ability. Brooks et al.\textsuperscript{[27]} utilized a battery of speech-language tests: preschool language scale-3, Minnesota child development inventory, Peabody picture vocabulary test, Goldman Fristoe, short-long sentence repetition task, and expressive vocabulary test. Through these, they rated the patients’ CI performance as fair and noted improvements in his speech and language abilities. Nevertheless, his communication abilities remained below age-appropriate level with approximately 60\% verbal and 40\% sign language use. Menezes et al.\textsuperscript{[31]} also stated the use of an array of speech-language tests before CI (for example, the Peabody picture vocabulary test), but none of the results from these tests were presented in the study. Audiological outcomes are summarized in

\[
\begin{array}{cccccccccccccc}
\text{Leenheer et al. (2008)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Santarelli et al. (2015)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Sinnathuray et al (2010)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Menezes et al. (2016)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Anderson et al. (2019)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Han et al. (2017)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Atigian et al. (2019)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Postelmers et al. (2006)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Goswamy et al. (2012)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Anzalone et al. (2018)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Kobayashi et al. (2020)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Brookes et al. (2020)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Miyamoto et al. (1999)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\text{Frewin et al. (2013)} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet \\
\end{array}
\]

Key. Green = Yes (low risk of bias); Red = No (high risk of bias); Yellow = unclear (unclear risk of bias); Gray = Not applicable

1. Were participants a representative sample selected from a relevant patient population?
2. Were the inclusion/exclusion criteria of participants clearly described?
3. Were participants entering the study at a similar point in their disease progression?
4. Was selection of patients consecutive?
5. Was data collection undertaken prospectively?
6. Were the groups comparable on demographic characteristics and clinical features?
7. Was the intervention (and comparison) clearly defined?
8. Was the intervention undertaken by someone experienced at performing the procedure?
9. Were the staff, place, and facilities where the patients were treated appropriate for performing the procedure?
10. Were any of the important outcomes considered (i.e., on clinical effectiveness, cost-effectiveness, or learning curves)?
11. Were objective outcome measures used, including satisfaction scale?
12. Was the assessment of main outcomes blind?
13. Was follow-up long enough (\(\geq 1\) year) to detect important effects on outcomes of interest?
14. Was information provided on non-respondents, dropouts?
15. Were the characteristics of withdrawals/dropouts similar to those that completed the study and therefore unlikely to cause bias?
16. Was length of follow-up similar between comparison groups?
17. Were the important prognostic factors identified?
18. Were the analyses adjusted for confounding factors?
### Table 5. Patient Reported Outcome Measures

Only 2 studies used PROMs\(^{33,30}\). Frewin et al.\(^{33}\) administered 2 questionnaires preoperatively and postoperatively. Of these, 1 was a standardized non-disease specific measure, the EuroQol, and the other was a disease specific questionnaire which measured hearing-related quality of life, the Nijmegen cochlear implant questionnaire (NCIQ). No improvements were demon-

### Table 5. Audiological outcomes

| Study                     | Preoperative data                                                                 | Postoperative data                                                                 | Overall benefit (subjective assessment) | Follow-up |
|---------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------|-----------|
| Leenheer et al. (2008)    | Pure-tone audiometry: At 0.5-1.2 Hz = 78 dB HL (right side) and 105 dB HL (left side) | Pure-tone audiometry: Average Pure-tone threshold of 40 dB HL.                    | Significant benefit                    | 24m       |
|                           | Speech perception scores: • NVA, CVC, phoneme score = 25% at 105 dB SPL testing both ears separately. Using hearing aids, she achieved monaural maximum recognition scores of 48% and 27% at 70 dB SPL in the right and left ears, respectively. Communication mode: Communication was extremely difficult, and she was unable to use the telephone. | Speech perception scores: • (NVA, CVC, phoneme score) of 86.5% at 70 dB SPL after implantation. Communication mode: The postimplantation communication mode was oral. The patient was able to use the telephone with familiar voices. | 7 out of 8 benefited. | 12m       |
| Santarelli et al. (2015)  | Pure-tone audiometry: Mean PTA (R/L): 50.5/48.6 dB Mean Low frequency (average thresholds at 0.5,1,2 kHz) = 63.3/63.4 dB (R/L) Mean High frequency (average thresholds at 4,8 kHz) = 74.1/60.5 dB (R/L) | Pure-tone audiometry: Mean PTA Aided threshold: 28.1 dB | 6 Months                               | Both did not benefit | 6-48m     |
|                           | Speech perception scores: 9 Overall, mean open-set disyllable recognition scores measured in quiet increased from 16% in the pre-implant condition to 72% as evaluated after 1-years’ experience with the cochlear implant. Differently from all others, Subject 9 had no improvement of speech perception with cochlear implant use (paired t-test, p<0.01). In six patients speech perception was also evaluated in the presence of background noise at two different signal- to-noise ratios (+10, +5). For each level of noise, open-set recognition scores significantly increased after 1 year of cochlear implant use compared with the pre-implant condition (p<0.01). Considering individual scores, all the OPA1-M patients improved performances when using the cochlear implant. | Speech perception scores: Patient 2: BKB score: 25% in quiet and 3% in noise 9 Months Speech perception scores: • Patient 1 o BKB score: L = 0, R = 0, R + L = 0 o CUNY Score: L = 8, R = 10, R + L = 22 | 6 Months                               | Both did not benefit | 6-48m     |
|                           |                                                                                   | Speech perception scores: • Patient 1 o BKB score: L = 0, R = 0, R + L = 0 o CUNY Score: L = 8, R = 10, R + L = 22 |                                                                                   | Both did not benefit | 6-48m     |
|                           |                                                                                   | Speech perception scores: • Patient 1 o BKB score: L = 0, R = NR, R + L = NR o CUNY Score: L = NR, R = NR, R + L = 15 |                                                                                   | Both did not benefit | 6-48m     |
|                           |                                                                                   | Pure-tone audiometry: Patient 1: Aided HR (dB): L = 42, R = NR |                                                                                   | Both did not benefit | 6-48m     |
Overall benefit (subjective assessment) | Follow-up
---|---
Menezes et al. (2016) | Significant benefit | 6-12m

| Study | Preoperative data | Postoperative data | Follow-up |
|---|---|---|---|
| Menezes et al. (2016) | Pure-tone audiometry: R - moderate to severe HL, L - severe-to-profound HL. Poor discrimination without visual cues. Speech perception scores: • DeVault common phrases = 35% words correct (Left HA), not tested with right HA • BKB sentences = 46% words correct (right HA), not tested with left HA • Manchester Junior = 10% words correct, 45% phonemes correct (Left HA), not recorded for right HA • CVC words = 40% words correct, 69% phonemes correct (Right HA), not recorded for left HA • GASP phoneme detection and imitation = Vowel detection: 100% (L HA), 100% (R HA) Consonant detection: 66% (L HA), 100% (R HA) Vowel identification: 18% (L HA), 66% (R HA) Consonant identification: 16% (L HA), 50% (R HA) | 6 Months Speech perception tests: • DeVault common phrases: 85% words correct • BKB sentences: 78% words correct • Manchester Junior: 65% words correct, 81% phonemes correct • CVC words: 40% words correct, 65% phonemes correct • GASP phoneme detection and imitation: Vowel detection: 100% Consonant detection: 100% Vowel identification: 100% Consonant identification: 58% | 6-12m |
| Anderson et al. (2019) | Pure-tone audiometry: At 2 kHz, 4kHz = Patient 1 = 80, 86 dBHL / Patient 2 = 80, 95 dBHL / Patient 3 = 90, 90 dBHL Speech perception scores: • CAP = Patient 1 = 2 / Patient 2 = 3 / Patient 3 = 2 Communication mode: Patient 1 = Exclusively via sign language Patient 2 = Patients condition requires ventilation via tracheostomy for 18 hours a day. With access to only environmental sounds. She had no speech discrimination. Patient 3: Unable to pronounce any clear words, and deemed too old to acquire spoken language | Pure-tone audiometry: At: 2 kHz, 4kHz = Patient 1 = 40, 40 dBHL / Patient 2 = 30, 25 dBHL / Patient 3 = 20, 30 dBHL Speech perception scores: • CAP: Patient 1 = 5 / Patient 2 = 5 / Patient 3 = 3 • ASSE = Patient 1 = 40-45dB / Patient 2 and 3 were not cognitively ready Duration of daily use in hours (via data logging system): Patient 1 = 4.9 / Patient 2 = Fulltime / Patient 3 = 10 PROM: • BAPP o Usage = Pt. 1 = Wears CI all the time; Pt. 2 = Wears CI all the time o Willingness = Pt. 1 = Very keen to wear CI; Pt. 2 = Very keen to wear CI o Behavior = Pt. 1 = Slightly better; Pt. 2 = Much better o Contentment = Pt. 1 = Much better; Pt. 2 = Much better o Communication = Pt. 1 = Much better; Pt. 2 = Much better o Learning = Pt. 1 = Slightly better; Pt. 2 = Much better o Getting on with friends = Pt. 1 = Slightly better; Pt. 2 = Much better | |
Table 5. Audiological outcomes (Continued)

| Study                     | Preoperative data                                                                 | Postoperative data                                                                 | Overall benefit (subjective assessment) | Follow-up |
|---------------------------|-----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------|-----------|
|                           |                                    | Satisfaction (recommended to those in a similar situation) = Pt. 1 = Yes; Patient 2 = Yes Communication mode: Patient 1 = Improved access to sound and improved auditory performance. Recently developed a spoken vocabulary using a wide range of single words. Patient 2 = Improved access to sound and improved auditory performance. She can identify a wide variety of environmental sounds and speech sounds consistently. Due to tracheostomy ventilation, speech is not an appropriate goal. Patient 3: He has developed a small spoken vocabulary. | All 3 showed modest benefit | 12m (except for patient 3, patients 3’s postoperative data was taken at an unspecified time after his surgery and as it was a recent case, they have not completed the 12-month follow-up data) |
| Han et al. (2017)         | Pure-tone audiometry: Average pure-tone thresholds from 0.5 to 4kHz = 59 dB (right) 40dB (left). Bilateral severe low frequency sensorineural hearing loss. Speech perception scores: • SDS: Right Ear = 8% at 100dB, Left ear 24% and 78dB • K-CID: unaided = 36%, aided with HA = 0% • PB word: 11.1% • Spondee word: 5% | 3 Months Speech perception scores: • K-CID: 94% • PB word: 55.6% / • Spondee word: 80% | Significant benefit | 3-6m |
| Atilgan et al. (2019)     | Pure-tone audiometry: R. Thresholds: 500Hz-85dB, 1kHz-45dB, 2kHz-20dB, 4kHz-15dB, 6kHz-60dB, 8kHz-20dB L. Thresholds: 500Hz-65dB, 1kHz-60dB, 2kHz-35Hz, 4kHz-15dB, 6kHz-65dB, 8kHz-10dB Speech perception scores: • Phonetically balanced word discrimination test 14: 0% | Pure-tone audiometry: Patient was followed up regularly with free field pure-tone audiometry, and her behavioral pure-tone thresholds were within range of 20-40dB HL after 1 year of CI use. Speech perception scores • Phonetically balanced word discrimination test 14 Activation: 50%, 3 months: 52%, 6 months: 76%, 1 year: 80%. • Turkish Matrix Sentence test (assessing her speech understanding in noise performance) = 50% speech reception threshold at 7.4 dB SNR after one year of CI usage. Other: Music perception abilities were also evaluated using T-CAMP. The subject scored 2,41 semitones on a pitch direction discrimination subtest and scored 45.83% and 8.33% on timbre and melody recognition subtests, respectively. | Significant benefit | 3-12m |
| Postelmans et al. (2006)  | Pure-tone audiometry: Showed severe, bilateral sensorineural hearing loss. Unaided pure-tone average thresholds were 95 dB for the left ear and 92.5 dB for the right ear. Speech perception scores: • The maximal discrimination scores were 30% at 75 dB in the left ear and 50% at 75 dB in the right ear. | Pure-tone audiometry: Average threshold for the right ear of 30 dB. Speech perception scores: • Maximal discrimination scores of 59% at 60 dB in the implanted ear. | Modest Benefit | 6m |
Table 5. Audiological outcomes (Continued)

| Study                           | Preoperative data                                                                 | Postoperative data                                                                 | Overall benefit (subjective assessment) | Follow-up |
|--------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------|-----------|
| Goswamy et al. (2012)           | Pure-tone audiometry: R. Thresholds: 250Hz-80dB, 500Hz-70dB, 1kHz-60dB, 2kHz-65dB, 4kHz-70dB | Pure-tone audiometry: PTA (implanted ear): 1 week = dead ear, 2 months = dead ear, 9 months = dead ear, 21 months = dead ear | Significant Benefit                  | 1 wk-21m  |
|                                | L. Thresholds: 250Hz-90dB, 500Hz-80dB, 1kHz-85dB, 2kHz-65Hz, 4kHz-80dB              | Speech perception scores: • BKB Open-set discrimination (quiet): 1 week = 0%, 2 months = 0%, 9 months = 53%, 21 months = 54% |                                        |           |
|                                | Speech perception scores: • CUNY (with lip reading) = 15%                           | • CUNY (with lip reading) + aid/implant = 40%                                     |                                        |           |
|                                | Communication Mode: R. Thresholds: 250Hz-90dB, 500Hz-80dB, 1kHz-85dB, 2kHz-65Hz, 4kHz-80dB | Communication Mode: R. Thresholds: 250Hz-90dB, 500Hz-80dB, 1kHz-85dB, 2kHz-65Hz, 4kHz-80dB | Communication Mode: Relied on lip-reading to communicate. |            |
|                                | L. Thresholds: 250Hz-90dB, 500Hz-80dB, 1kHz-85dB, 2kHz-65Hz, 4kHz-80dB              | L. Thresholds: 250Hz-90dB, 500Hz-80dB, 1kHz-85dB, 2kHz-65Hz, 4kHz-80dB             |                                        |           |
|                                | Speech perception scores: • BKB Open-set discrimination (quiet): 1 week = 0%, 2 months = 0%, 9 months = 53%, 21 months = 54% | Speech perception scores: • BKB Open-set discrimination (Manchester average): 1 week = 49%, 2 months = 71%, 9 months = 77%, 21 months = 72% |                                        |           |
|                                | • CUNY (with lip reading) = 15%                                                     | • CUNY (with lip reading) + aid/implant: 1 week = 41%, 2 months = 72%, 9 months = 94%, 21 months = Not tested |                                        |           |
|                                | Speech perception scores: • CUNY (with lip reading) Manchester average: 1 week = 68%, 2 months = 89%, 9 months = 83%, 21 months = 80% | Communication Mode: Relied on lip-reading to communicate. |                                        |            |
| Anzalone et al. (2018)          | Pure-tone audiometry: Profound SNHL in the left ear and moderate-severe SNHL in right ear. | Speech perception scores: • CNC Phoneme = 53%                                      | Modest benefit                         | 7m        |
|                                | Speech perception scores: • CNC Phoneme = 0%                                       | • AzBio sentence = 32%                                                           |                                        |           |
|                                | • A2Bio sentence = 0%                                                              | At an 18-month phone follow-up, he reports improving subjective benefit and consistent usage of the device |                                        |           |
| Kobayashi et al. (2020)         | Pure-tone audiometry: Patient 1: R. Thresholds: 250Hz-50dB, 500Hz-95dB, 1kHz-105dB, 2kHz-105dB, 4kHz-95dB, 8kHz-90dB | Pure-tone audiometry: Patient 1: 1kHz-50dB, 2kHz-45dB, 4kHz-45dB, 8kHz-45dB | Modest benefit                         |            |
|                                | Patient 2: R. Thresholds: 250Hz-110dB, 500Hz-105dB, 1kHz-105dB, 2kHz-95dB, 4kHz-105dB, 8kHz-85dB | Patient 2: Bilateral: 250Hz-35dB, 500Hz-30dB, 1kHz-35dB, 2kHz-60dB, 4kHz-30dB, 8kHz-50dB | Not specified when follow-up period was for PTA measurements. |           |
|                                | L. Thresholds: 250Hz-95dB, 500Hz-100dB, 1kHz-100dB, 2kHz-95Hz, 4kHz-90dB, 8kHz-80dB | Speech perception scores: Patient 1: Maximum discrimination score = 30% (70dB) in quiet 15m after right-sided CI. Maximum discrimination scores then improved to 45% (60dB) in quiet 6m after bilateral CI (which took place in total 18m after his first CI). | Speech discrimination follow-up periods were: Patient 1: 15m after right-sided CI and 6, after sequential bilateral CI. Patient 2: 10 months for patient 2 |           |
|                                | Speech perception scores: Patient 2: Maximum discrimination score improved to 5% (50dB) in quiet 10 months after CI on both sides Communication Mode: Patient 1: subject can make a conversation in daily life Patient 2: she did not have enough ability to have a conversation by sound only | Voice: Patient 2: Maximum discrimination score improved to 5% (50dB) in quiet 10 months after CI on both sides Communication Mode: Patient 1: subject can make a conversation in daily life Patient 2: she did not have enough ability to have a conversation by sound only |                                        |           |
| Brookes et al. (2007)           | Pure-tone audiometry: Aided testing showed mild-to-moderate loss for both pure tones and speech reception Other (speech and language tests): • Preschool language scale-3 (age 45 months): Auditory compensation = 1.1st% (25-month equiv.), | Pure-tone audiometry: Patient 1: 1kHz-50dB, 2kHz-45dB, 4kHz-45dB, 8kHz-45dB | Modest benefit                         | 12-24m    |
|                                | 12 Months Speech perception scores: • CID four choice spondee test = 54% correct | Other (speech and language tests): • Preschool language scale-3 (age 60 |                                        |           |
Table 5. Audiological outcomes (Continued)

| Study                     | Preoperative data                                                                 | Postoperative data                                                                 | Overall benefit (subjective assessment) | Follow-up |
|---------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------|-----------|
|                           | Expressive communication = 1% (20-month equiv.), Total language score = 1% (23-month equivalent) | (29-month equiv.), Expressive communication = 1% (23-month equivalent), Total language score = 1% (26-month equivalent) |                                        |           |
|                           | • Minnesota child developmental inventory:                                       | • Peabody picture vocabulary test: Std score 40 < 1st% (<24-month equiv.)         |                                        |           |
|                           | Expressive = 22-month equiv., Comprehension = 21-month equiv., Situation comprehension = 30-month equiv. | 24 Months Pure-tone audiometry: Unaided pure-tone thresholds in the severe-to-profound hearing loss range Speech perception scores • CID source choice spondee test = 92% correct • Vowel feature test = 43% correct Other (speech and language tests): • Preschool language scale-3 (age 72 months): Auditory compensation = 1st% (39-month equiv.), Expressive communication = 1% (30-month equiv.), Total language score = 1% (36-month equivalent) • Peabody picture vocabulary test: Std score 61 < 1st% (<36-month equiv.) • Short-long sentence repetition Task: 34% phonemes and 11% words pronounced correctly • Expressive vocabulary test: 58th% (78-month equiv.) |                                        |           |
| Miyamoto et al. (1999)    | Pure-tone audiometry: R. Thresholds: 500Hz-105dB, 1kHz-100dB, 2kHz-85dB, 4kHz-85dB, 8kHz-80dB | Patient: Unaided PTA average: 97dB Control: Mean Unaided PTA average: 103dB Speech perception scores: • Minimal Pairs Test o Patient: mean closed-set vowel recognition score = 77% o Control: mean closed-set vowel recognition score = 89% o Patient: mean closed-set consonant recognition score = 72% o Control: mean closed-set consonant recognition score = 82% • Open-set word recognition (PBK): o Patient: 0% of the words and 0% of the phonemes were identified correctly o Control: 24% of the words and 54% of the phonemes were identified correctly 12 Months Speech perception scores: • Minimal Pairs Test o Patient: mean closed-set vowel recognition score = 82% o Control: mean closed-set vowel recognition score = 92% o Patient: mean closed-set consonant recognition score = 70% | Modest benefit 6-12m |           |
Stratified across the 5 EuroQol domains (mobility, self-care, usual activities, anxiety, and depression). However, the NCIQ noted improvements across the physical domain, psychological domain, and significant improvements in the social domain. Anderson et al. used a proxy PROM by assessing parental perception for 2 of their CI recipients using the Brief Assessment of Parental Perception (BAPP) questionnaire. Both sets of parents reported benefit from the CI and recommended it for other patients with BVVL in a similar bracket. The BAPP was not administered to the third patient as the patient had only been recently implanted at the time.
of publication.

**Surgical Outcomes**

A total of 5 studies reported no surgical complication\[21-27,33\]. Sinnathurai et al.\[35\] reported a postoperative complication in their male patient, where on extubation he suffered a prolonged apneic episode, which required reintubation and transfer to the intensive care unit for 24 hours. Fortunately, he made a satisfactory recovery and was discharged after 3 days. The remaining 8 studies made no explicit comments regarding the absence or occurrence of any surgical complications.

**DISCUSSION**

This systematic review and narrative synthesis reports on outcomes of CI in postsynaptic ANs. The review aimed to understand and clarify the relationship between the site of the lesion and expected outcomes following CI. To the best of the authors' knowledge, this is the first systematic review on this topic. Overall, across the 14 studies identified in this review, there was a trend toward good post-CI outcomes with 22 of the total 25 patients displaying modest to significant benefit. However, this was not universally the case, and 2 of the 3 patients who had no observed benefit post CI were siblings from the same study by Sinnathurai et al.\[35\] and had a diagnosis of BVVL syndrome. They underwent CI at 41 and 45 years of age and the authors concluded the poor outcomes were likely related to retrocochlear degeneration with probable involvement of the central auditory pathway. Furthermore, a contributing factor to the poor outcomes was the long period of auditory deprivation before patients had the intervention. Comparatively, at 12 months follow-up, the 3 BVVL patients from the study by Anderson et al.\[28\] (mean age 7.9 years at CI) and the single patient from the study by Menezes et al.\[31\] (mean age 10.5 years at CI) all reported significant benefit from CI. All 4 of these patients were diagnosed early and had received oral riboflavin treatment as part of their pre-CI management. In all four of these patients, the riboflavin treatment was noted to have a modest to profound effect in improving general symptoms and delaying the decline in hearing loss\[23,31\]. These differences of earlier intervention could explain why limited benefit was achieved by the patients in the study by Sinnathurai et al.\[35\].

The other patient who had no observed benefit from CI was from the study by Santarelli et al.\[37\] and had a diagnosis of DOA+. Referred to as Subject 9, the patient was the only 1 of 5 who reportedly had not undergone CI at their department. At the time of his first evaluation, he had already been using a cochlear implant for 2 years. Given Subject 9’s poor performance, he underwent an integrity testing of his device and a computed tomography scan which showed no cochlear malformation. All the other 7 patients with DOA+ in this study were noted to have significant improvements in their one-year post-CI speech perception tests. However, follow-up data for Subject 9 was presented at a different stage from the rest of the group, making a direct comparison difficult. It could be that Subject 9 had also made significant improvements in speech perception performance at one-year post CI, but beneficial effects had reached a limit. The answers regarding the lack of reported benefit will remain inclusive without Subject 9’s baseline data.

**Establishing the relationship between postsynaptic lesion site and CI outcome**

The findings from this review are not sufficient to meaningfully address the impact of a postsynaptic lesion site in AN on CI outcomes. There are numerous methodological limitations in the eligible studies that precluded synthesis of an established narrative. First, the studies were all retrospective case reports or small volume case series. These observational/descriptive study designs limit the robustness of any assessment of outcomes. Studies of this nature can be subjected to significant selection and reporting biases. Furthermore, observational studies are prone to confounding variables which can partially or completely contribute to the observed results\[37\]. Aside from the study design, a major limitation of these studies was the significant heterogeneity across reported outcome measures and follow-up periods, with some studies reporting post-CI outcomes at 2 and 6 months and others at 12 months.

Furthermore, this review was only able to identify studies relating to 6 of the 11 postsynaptic AN pathologies identified in the scoping searches. With only 6 postsynaptic AN conditions, and a collective sample size of 25, the results may not be completely representative of the whole subgroup. There is also a lack of understanding and debate regarding the exact pathological sites of CAPOS and BVVL syndrome. Through advancements in diagnostic capabilities and our understanding of the peripheral auditory system, these issues should be able to be better addressed.

**Clinical and Research Consequences**

Although the decision to fit a patient with an implant is made on an individual case basis, there is great value to be obtained from sub-grouping sets of patients. This form of stratified medicine will help with clinical decision making as well as health care service planning and purchasing. Our work, though not perfect, is a step along this path.

In order to do achieve this, we need to develop improved diagnostic tools (genetic and audiometric) to accurately define the site of the lesion(s) and the degree of dysfunction. Potential examples include frequency-specific round window electrocochleography (ECochG). McMahon et al.\[38\] who investigated the site of lesion in AN demonstrated that presynaptic and postsynaptic type of AN existed, and round window ECochG had the potential to identify different subtypes of AN. Rance et al.\[19\] highlights the possible use of diffusion tensor imaging (DTI) to better characterize white matter structures.

Alongside improved diagnostics, reporting of CI outcomes in all patient groups should be improved so that patterns can be better identified. This step might prove difficult given the expense of CI, rarity of these conditions, and their genetic and phenotypical heterogeneity. Therefore, observational design studies will continue to predominate. As Humphriss et al.\[19\] in their systematic review on CI effect on speech recognition in children with ANSD, suggested the best feasible alternative is the use of broad multicenter longitudinal studies where all patients with AN are prospectively recorded regardless of treatment.

Development of alternative novel treatment strategies could play a role in improving the lives of these patients. Given that approximately 40% of patients with AN have a genetic basis, an area receiving increased attention is gene therapy using adeno-associated virus
vectors. In a preclinical study in mice with PJVK associated AN (presynaptic AN), the researchers found gene therapy was able to restore the cochlear function and improve their hearing thresholds. However, bridging these preclinical trials to humans is going to take a long time, with estimates of around 20 years.

Finally, there needs to be more appropriate and standardized outcome measures to identify improvements in these complex patients. The need for this is exemplified in a case report by Miyamoto et al. about CI in a 10-year-old child with FRDA. During their clinical assessment, they were unable to administer the complete battery of tests as the patient’s condition resulted in severely diminished visual ability and quick fatigability from testing. Although audiological and speech perception measures are key in AN, a full range of social/emotional developmental outcomes should be measured, possibly through health-related quality of life (HRQoL) questionnaires. A systematic review by Lin et al. exploring HRQoL in pediatric CI patients concluded that HRQoL data would facilitate a better understanding of candidacy criteria, rehabilitative needs of the children, and better service provision.

CONCLUSION
Hearing outcomes after CI in postsynaptic ANs, although variable, are generally good. The majority of patients in this review received some form of benefit from their baseline. However, the small sample size and methodological limitations are a cause for caution. In future, the development of a clearer stratification system into pre, post, and central AN would have clinical and academic benefits. Further research is required to understand AN pathophysiology and develop better diagnostic tools (audiological and genetic) for more accurate identification of lesion sites. Multicenter longitudinal studies with standardized comprehensive outcome measures including HRQoL data will be key in establishing a better understanding of short and long-term post-CI outcomes.

REFERENCES
1. Starr A, Picton TW, Sining y, Hood LJ. Berlin CI. Auditory neuropathy. Brain 1996; 119: 741–53. [Crossref]
2. Berlin CI, Morlet T, Hood LJ. Auditory neuropathy/dysynchrony: Its diagnosis and management. Pediatr Clin North Am 2003; 50: 331-40. [Crossref]
3. Rance G, Starr A. Pathophysiological mechanisms and functional hearing consequences of auditory neuropathy. Brain 2015; 138: 3141-58. [Crossref]
4. Penido RC, Isaac ML. Prevalence of auditory neuropathy spectrum disorder in an auditory health care service. Braz J Otorhinolaryngol 2013; 79: 429-33. [Crossref]
5. Rance G, Beer D, Cone-Wesson B, Shepherd R, Dowell R, King A, et al. Clinical Findings for a Group of Infants and Young Children with Auditory Neuropathy. Ear Hear 1999; 20: 238. [Crossref]
6. Foerst A, Beutner D, Lang-Roth R, Huttenbrink K-B, von Wedel H, Walger M. Prevalence of auditory neuropathy/synaptopathy in a population of children with profound hearing loss. Int J Pediatr Otorhinolaryngol 2006; 70: 1415–22. [Crossref]
7. Rance G. Auditory neuropathy/dysynchrony and its perceptual consequences. Trends Amplif 2005; 9: 1-43. [Crossref]
8. Santarelli R. Information from cochlear potentials and genetic mutations helps localize the lesion site in auditory neuropathy. Genome Med 2010; 2: 91. [Crossref]
9. Moser T, Starr A. Auditory neuropathy — neural and synaptic mechanisms. Nat Rev Neurol 2016; 12: 135-49. [Crossref]
10. Shearer AE, Hansen MR. Auditory synaptopathy, auditory neuropathy, and cochlear implantation. Laryngoscope Investig Otolaryngol 2019; 4: 429-40. [Crossref]
11. De Siati RD, Rosenzweig F, Gersdorff G, Greigore A, Rombaux P, Degouj N. Auditory Neuropathy Spectrum Disorders: From Diagnosis to Treatment: Literature Review and Case Reports. J Clin Med 2020; 9: 1074. [Crossref]
12. Tranebjærg L. Deafness-dystonia-optic neuropathy syndrome [Internet]. In: GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993–2020. 2003 Feb 6 [updated 2019 Nov 21; cited 2020 Jun 28]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK12126/ [Crossref]
13. Kabayashi M, Yoshida T, Sugimoto S, Terasihni M, Hara D, Kimata Y, et al. Cochlear implantation in patient with Charcot-Marie-Tooth disease. Auris Nasus Larynx 2020; 47: 7-14. [Crossref]
34. Miyamoto RT, Kirk KI, Renshaw J, Hussain D. Cochlear implantation in auditory neuropathy spectrum disorder. Laryngoscope 1999; 109: 181-5. [Crossref]
35. Anzalone CL, Nuhanovic S, Olund AP, Carlson ML. Cochlear Implantation in Charcot-Marie-Tooth Disease: Case Report and Review of the Literature. Case Rep Med 2018; 2018: 1760978. [Crossref]
36. Lu CY. Observational studies: a review of study designs, challenges and strategies to reduce confounding. Int J Clin Pract 2009; 63: 691-7. [Crossref]
37. McManus CM, Patuzzi RB, Gibson WPR, Sanil H. Frequency-specific electroocochleography indicates that presynaptic and postsynaptic mechanisms of auditory neuropathy exist. Ear Hear 2008; 29: 314-25. [Crossref]
38. Humphreiss R, Hall A, Maddocks J, Macleod J, Sawaya K, Midgley E. Does cochlear implantation improve speech recognition in children with auditory neuropathy spectrum disorder? A systematic review. Int J Audiol 2013; 52: 442-54. [Crossref]
39. Manchaiah VKC, Zhao F, Danesh AA, Duprey R. The genetic basis of auditory neuropathy spectrum disorder (ANSD). Int J Pediatr Otorhinolaryngol 2011; 75: 151-8. [Crossref]
40. Cheng YF, Wu CC, Ying-Chang LU, inventors. Method for treating an auditory neuropathy spectrum disorder. United States patent application US 16/586,768. 2020 Apr 2. Available from: https://patents.google.com/patent/US20200101122A1/en
41. Zhang W, Kim SM, Wang W, Cai C, Feng Y, Kong W, et al. Cochlear Gene Therapy for Sensorineural Hearing Loss: Current Status and Major Remaining Hurdles for Translational Success. Front Mol Neurosci 2018; 11: 221. [Crossref]
42. Lin FR, Niparko JK. Measuring health-related quality of life after pediatric cochlear implantation: A systematic review. Int J Pediatr Otorhinolaryngol 2006; 70: 1695-706. [Crossref]
43. Man PYW, Turnbull DM, Chinnery PF. Leber hereditary optic neuropathy. J Med Genet 2002; 39: 162-9. [Crossref]
44. Čeranić B, Luxon LM. Progressive auditory neuropathy in patients with Leber’s hereditary optic neuropathy. J Neurol Neurosurg Psychiatry 2004; 75: 626-30. [Crossref]
45. Starr A, Isaacson B, Michalewski HJ, Zeng FG, Kong YY, Beale P, et al. A dominantly inherited progressive deafness affecting distal auditory nerve and hair cells. J Assoc Res Otolaryngol 2004; 5: 411-26. [Crossref]
46. Schoen CJ, Emery SB, Thorne MC, Ammana HR, Sliwerska E, Arnett J, et al. Increased activity of Diaphanous homolog 3 (DIAPH3)/diaphanous causes hearing defects in humans with auditory neuropathy and in Dro sophila. Proc Natl Acad Sci 2010; 107: 13396-401. [Crossref]
47. Diaz-Horta O, Abad C, Sennaroglu L, Foster J, DeSmidt A, Bademci G, et al. ROR1 is essential for proper innervation of auditory hair cells and hearing in humans and mice. Proc Natl Acad Sci 2016; 113: 5993-8. [Crossref]
48. Zong L, Guan J, Ealy M, Zhang Q, Wang D, Wang H, et al. Mutations in apoptosis-inducing factor cause X-linked recessive auditory neuropathy spectrum disorder. J Med Genet 2015; 52: 523-31. [Crossref]
49. Živković MG, Zupančič A, Delgado-García D, Hinojosa-Hernández M, Palomino-Ramírez I. Laron syndrome. Cochlear Implants Int 2019; 20: 31-8. [Crossref]
50. Simon M, Richard EM, Wang X, Shahzad M, Huang VH, Qaiser TA, et al. Dominant optic atrophy. Orphanet J Rare Dis 2012; 7: 1-12. [Crossref]
51. Kovach MJ, Campbell KCM, Herman K, Waggoner B, Gelber D, Hughes LF, et al. Anticipation in a unique family with Charcot-Marie-Tooth syndrome and deafness: delineation of the clinical features and review of the literature. Am J Med Genet 2002; 108: 295-303. [Crossref]
52. Simon M, Richard EM, Wang X, Shahzad M, Huang VH, Qaiser TA, et al. Mutations of human NARS2, encoding the mitochondrial asparaginyl-tRNA synthetase, cause nonsyndromic deafness and Leigh syndrome. PLoS Genet 2015; 11: e1005097. [Crossref]
53. Quaranta A, Arslan E, Babighian G, Filipo R, Amadori M, Amoruso VA, et al. Impianto cocleare: protocolli di selezione e valutazione dei soggetti adulti. Acta Phoniatri Lat 1996; 18.
Appendix A

Search terms used for MEDLINE:
1) Cochlear implantation.mp. or Cochlear Implantation/
2) Cochlear implant.mp. or Cochlear Implants/
3) Auditory prosthesis.mp.
4) Cochlear prosthesis.mp.
5) Charcot-Marie-Tooth Disease.mp. or Charcot-Marie-Tooth Disease/
6) CMT.mp.
7) Hereditary Sensory and Motor Neuropathy
8) Friedreich's Ataxia.mp. or Friedreich Ataxia/
9) FRDA.mp.
10) Optic Atrophy.mp. or Optic Atrophy/
11) Autosomal dominant optic atrophy.mp. or Optic Atrophy, Autosomal Dominant/
12) OPA1.mp.
13) Kjer type optic atrophy.mp.
14) Dominant optic atrophy.mp.
15) ADOA
16) Deafness-dystonia-optic neuropathy syndrome.mp.
17) DDON
18) Dystonia/ or Mohr-Tranebjaerg syndrome.mp.
19) Optic Atrophy Hereditary, Leber/ or LHON.mp.
20) CAPOS.mp.
21) ATP1A3.mp
22) Brown-Vialetto-van-Laere Syndrome.mp.
23) BVVL.mp.
24) DIAPH3.mp.
25) Autosomal dominant non-syndrome hearing loss.mp.
26) Receptor Tyrosine Kinase-like Orphan Receptors/ or ROR1.mp.
27) Cowchock Syndrome.mp.
28) Apoptosis Inducing Factor/ or AIFM1.mp.
29) Leigh Syndrome.mp. or Leigh Disease/
30) NARS2.mp.
31) 1 OR 2 OR 3 OR 4
32) 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30
33) 31 AND 32