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Review

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[4,5,6]. 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.

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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[7]. 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.[3] 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[8,9]. 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[3]. 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[7,8]. Finally, in central ANs, the site of lesion is located at the brainstem level, including cerebello-pontine angle tumors, such as vestibular schwannomas and meningiomas[3]. Figure 1 demonstrates a schematic representation of these divisions.

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.

Postsynaptic ANs

Advancements in diagnostic tools such as electrocochleography and genetic sequencing have led to identification of a number of ANs as well as their sub-classification as either presynaptic, postsynaptic, or central. This classification is constantly evolving with the resolution of uncertainties regarding the precise site(s) of the lesions. A literature search led us to identify 11 postsynaptic ANs, and 6 of those 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.

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 presenting with moderate to severe hearing loss. The pathophysiology is thought to be due to degeneration of the terminal axons of the spiral ganglion neurons[10,11].

Deafness-dystonia-optic neuronopathy (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 cochlear, vestibular, and optic neurons.

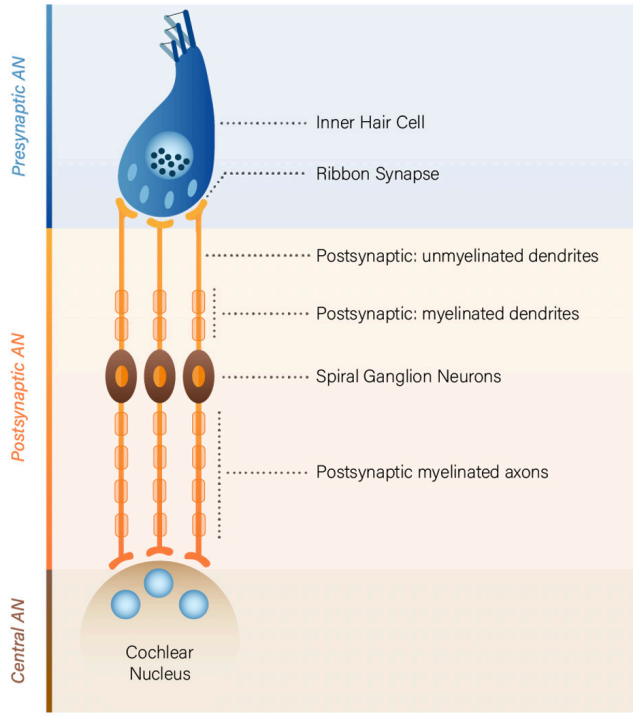

Figure 1. Overview of the peripheral auditory system showing the presynaptic, postsynaptic, and central sites of lesions associated with auditory neuropathy. Illustration inspired by Moser et al. 2016 [9]

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)

This table has been produced with the aid of tables from Shearer et al., 2019 and Santarelli et al., 2010[8,10].

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[10,11,12].

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[13]. These transporters are responsible for the cellular uptake of riboflavin, which is an essential component in oxidative metabolism and functional maintenance of the neurons[14]. BVVL is characterized by progressive pontobulbar palsy associated sensorineural deafness, facial weakness, and respiratory compromise[13,15].

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[16]. The NKAα3 plays a crucial role in the regulation of electrochemical gradients across the plasma membrane[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[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)[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[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[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[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[7]. 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[10]. 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[3,20]. 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. postimplantation audiometric 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-

sheet (Excel, Microsoft Corp, WA, USA).

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[28]; 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.

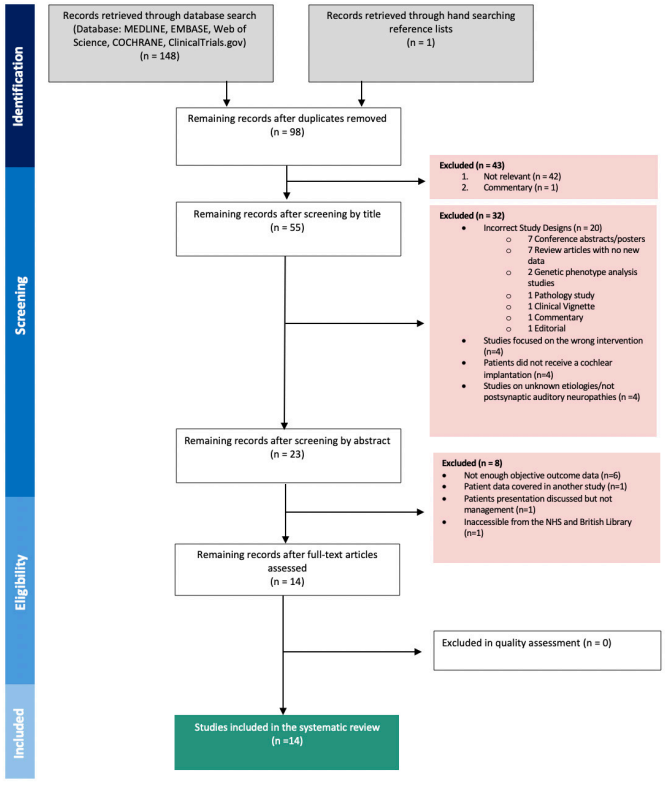

Figure 2. PRISMA Flow diagram

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[23,27]. 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[23,25–30,32–35], 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-Kowal-Bamford (BKB) Sentences[26,31,33,35], Nederlandse vereniging voor audiologie (NVA, Dutch) test[23], 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)[24], and Turkish matrix sentence test[32]. 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

							Outcome Measures Reported		
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	Nether-lands	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)

							Outcome Measures Reported		
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 neuronopathy syndrome	No	1	Yes	Yes: CID four choice spondee test, Vowel feature test	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	IV
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: No	IV
Frewin et al.	2013	England	Case Report (retrospective)	Friedreich's Ataxia	No	1	Yes	Yes: BKB	PROM: 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 = 5 / Pt 9 = 15	33 (5-48)	4 subjects carried the R445H mutation, not stated which patients though	NR	Insertion Site: 6 Right Ear (PT ID: 1,3,4,5,7,8) 2 Left Ear (2,9) Cochlear implant device: 7 C124RE (PT ID: 1,2,3,4,5,7,8) 1 HiRes90K (Pt. ID: 9) Full insertion: NR Surgical Complication: NR Rehabilitation details: NR

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
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. Full insertion: Yes 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
Menezes et al.	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. 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

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
								and hearing thresholds. HA werealso trialed, but pt. received no benefit. Pt 3 – Riboflavin treatment commenced ~ 1 month after the onset of hearing loss. This resulted an improvement in mobility however, despite early treatment he did not have improved hearing thresholds. HA were also trialed, but patient received limited benefit	
Han et al.	2017	CAPOS Syndrome	1 (1)	1 Female	Hearing loss began in her teenage years	24 (24)	WES identified a 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		

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
							3 of the PMP22 gene. This novel mutation resulted in a heterozygous valine to phenylalanine substitution at codon 65 (Val65Phe)	Hearing Aids at age 29 but no reported benefit	Insertion Site: Right ear Cochlear implant device: Advanced Bionics HiRes 90K R Full insertion: Yes Surgical Complication: No postoperative complications occurred Rehabilitation details: NR
Goswamy et al.	2012	Charcot-Marie-Tooth disease type 1A	1 (1)	1 Male	Patient considered himself to be deaf from early in his firth 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)	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)	1 Male 1 Female	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)	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 kB 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
							consistent with the diagnosis of XLA and DDON Syndrome. Further genetic testing s howed that the mother had 2 normal copies of the BTK gene, indicating a de novo mutation in the patient	he received until a CI	Insertion Site: Right ear Cochlear implant device: Advanced Bionics HiRes 90K Full insertion: NR Surgical Complication: No postoperative complications occurred Rehabilitation details: Following implantation, the patient was followed in a regular basis by the University of Iowa's children's cochlear implant program.
Miyamoto et al.	1999	Friedreich's Ataxia	1 (1)	1 Male	Referred at 4-year-old presenting with mild hearing loss in the right and moderate loss in the left	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 see. (2) Course of prednisolone therapy – resulted in a 115-dB improvement in the right ear for 500 and 1000Hz	Insertion Site: Unilateral (NR which ear) Cochlear implant device: Nucleus 22 Full insertion: NR Surgical Complication: NR Rehabilitation details: NR
Frewin et al.	2013	Friedreich's Ataxia	1 (2)	1 Female	Diagnosed with FRDA at age 10, age at hearing loss not reported	41 (41)	NR	Hearing Aid were trialed	Insertion Site: Bilateral (sequential, right side first and then left side 8 months afterwards) Cochlear implant model: Right side = Nucleus CI512; Left side = Nucleus Freedom Contour Advance implant Full insertion: Yes Surgical Complication: No postoperative complications occurred 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 ppointments were made to informally monitor progress and consolidating equipment skills.

NR: Not Reported/ Not specified; SNHL: sensory neural hearing loss; WES: Whole exome sequencing

Table 4. Brazzelli Risk of Biased Assessment

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Leenheer et al. (2008)	R	R	G	R	R	G	G	Y	Y	G	G	R	G	R	G	Gr	G	R
Santarelli et al. (2015)	G	Y	R	Y	R	G	G	Y	Y	G	G	R	G	R	G	G	G	R
Sinnathuray et al (2010)	R	R	R	Y	R	R	G	Y	Y	G	G	R	G	R	G	Gr	G	R
Menezes et al. (2016)	R	R	G	R	R	G	G	Y	Y	G	G	R	G	R	G	Gr	G	R
Anderson et al. (2019)	R	R	G	Y	R	R	R	Y	Y	G	G	R	R	R	G	Gr	G	R
Han et al. (2017)	R	R	G	R	R	G	R	Y	Y	G	G	R	R	R	G	Gr	G	R
Atılgan et al. (2019)	R	R	G	R	R	G	G	Y	Y	G	G	R	G	R	G	Gr	G	R
Postelmans et al. (2006)	R	R	G	R	R	G	G	Y	Y	G	R	R	R	R	G	Gr	G	R
Goswamy et al. (2012)	R	R	G	R	R	G	G	Y	Y	G	G	R	G	R	G	Gr	G	R
Anzalone et al. (2018)	R	R	G	R	R	G	G	Y	Y	G	G	R	R	R	G	Gr	G	R
Kobayashi et al. (2020)	R	R	G	Y	R	R	G	Y	Y	G	R	R	R	R	G	Gr	G	R
Brookes et al. (2020)	R	R	G	R	R	G	G	Y	Y	G	G	R	G	R	G	Gr	G	R
Miyamoto et al. (1999)	R	R	G	R	R	G	R	Y	Y	G	G	R	G	R	G	G	G	R
Frewin et al. (22013)	R	R	G	R	R	G	G	Y	Y	G	G	R	R	R	G	Gr	G	R

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 (≥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?

validated instrument. Santarelli et al.[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[26,28,34]. Goswamy et al.[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.[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.[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. Brookes et al.[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.[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

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) 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.	Pure-tone audiometry: Average Pure-tone threshold of 40 dB HL. 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.	Significant benefit	24m
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 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.	7 out of 8 benefited.	12m
Sinnathuray et al. (2010)	Pure-tone audiometry: Unaided HT (dB): L = 99, R=96 Aided HR (dB): L = 66, R = 65 Speech perception scores: • Patient 1 o BKB score: L = 1, R = 0, R + L = 5 o CUNY Score: L =13, R = 7, R+L = NR • Patient 2: NR	6 Months 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 21 Months 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 48 Months Pure-tone audiometry: Patient 1: Aided HR (dB): L =42, R = NR	Both did not benefit	6-48m (Patient 1 presented first, and they only performed extensive tests on him.)

Table 5. Audiological outcomes (Continued)

Study	Preoperative data	Postoperative data	Overall benefit (subjective assessment)	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% 12 Months Speech perception tests: • DeVault common phrases: NT • BKB sentences: 94% words correct with CI only, 82% with CI and HA, 70% when recorded audio • Manchester Junior: NR • CVC words: 52% words correct, 75% phonemes correct (CI only), 72% words correct, 89% phonemes correct (CI + HA) • GASP phoneme detection and imitation: Vowel detection: 100% Consonant detection: 100% Vowel identification: 100% Consonant identification: 83%	Significant benefit	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
		o 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% 6 Months Speech perception scores: • K-CID: 100% • PB word: 83.3% • Spondee: 95%	Significant benefit	3-6m
Atılgan 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 L. Thresholds: 250Hz- 90dB, 500Hz-80dB, 1kHz-85dB, 2kHz-65Hz, 4kHz-80dB Speech perception scores: • BKB Open-set discrimination = 0% • CUNY (with lip reading) = 15% • CUNY (with lip reading) + aid/implant = 40% Communication Mode: Relied on lip-reading to communicate.	Pure-tone audiometry: PTA (implanted ear): 1 week = dead ear, 2 months = dead ear, 9 months = dead ear, 21 months = dead ear Speech perception scores: • BKB Open-set discrimination (quiet): 1 week = 0%, 2 months = 0%, 9 months = 53%, 21 months = 54% • BKB Open-set discrimination (Manchester average): 1 week = 49%, 2 months = 71%, 9 months = 77%, 21 months = 72% • CUNY (with lip reading) + aid/implant: 1 week = 41%, 2 months = 72%, 9 months = 94%, 21 months = Not tested • CUNY (with lip reading) Manchester average: 1 week = 68%, 2 months = 89%, 9 months = 83%, 21 months = 80%	Significant Benefit	1 wk-21m
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 = 0% • AzBio sentence = 0%	Speech perception scores: • CNC Phoneme = 53% • AzBio sentence = 32% At an 18-month phone follow-up, he reports improving subjective benefit and consistent usage of the device	Modest benefit	7m
Kobayashi et al. (2020)	Pure-tone audiometry: • Patient 1 R. Thresholds: 250Hz-50dB, 500Hz-95dB, 1kHz-105dB, 2kHz-105dB, 4kHz-95dB, 8kHz-90dB L. Thresholds: 250Hz-55dB, 500Hz-95dB, 1kHz-105dB, 2kHz-100Hz, 4kHz-90dB, 8kHz-75dB • Patient 2 R. Thresholds: 250Hz-110dB, 500Hz-105dB, 1kHz-105dB, 2kHz-95dB, 4kHz-105dB, 8kHz-85dB L. Thresholds: 250Hz-95dB, 500Hz-100dB, 1kHz-100dB, 2kHz-95Hz, 4kHz-90dB, 8kHz-80dB Speech perception scores: • Patient 1: The maximum discrimination score was 0% • Patient 2: Not specified Communication Mode: Patient 1: difficulty to communicate only by sound Patient 2: subject would use writing and lip reading	Pure-tone audiometry: • Patient 1 1kHz-50dB, 2kHz-45dB, 4kHz-45dB, 8kHz -45dB L. Thresholds: 250Hz-55dB, 500Hz-45dB, 1kHz-45dB, 2kHz-50Hz, 4kHz-50dB, 8kHz-35dB • Patient 2 Bilateral: 250Hz-35dB, 500Hz-30dB, 1kHz-35dB, 2kHz-60dB, 4kHz-30dB, 8kHz-50dB 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). • 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	Modest benefit	Not specified when follow-up period was for PTA measurements. 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
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 = 1st% (25-month equiv.),	12 Months Speech perception scores: • CID four choice spondee test = 54% correct Other (speech and language tests): • Preschool language scale-3 (age 60	Modest benefit	12-24m

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) • Minnesota child developmental inventory: Expressive = 22-month equiv., Comprehension = 21-month equiv., Situation comprehension = 30-month equiv.	months): Auditory compensation = 1st% (29-month equiv.), Expressive communication = 1% (23-month equiv.), Total language score = 1% (26-month equivalent) • Peabody picture vocabulary test: Std score 40 < 1st% (<24-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% (38-month equivalent) • Peabody picture vocabulary test: Std score 61 < 1st% (<35-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 L. Thresholds: 500Hz-100dB, 1kHz-100dB, 2kHz-90dB, 4kHz-80dB, 8kHz-95dB Speech perception scores: • Minimal Pairs Test score (Control) mean closed-set vowel recognition score = 74% and mean closed-set consonant recognition score = 61% Patient did not have this test preimplantation as it was very taxing on him • Open-set word recognition (PBK): o Patient = 4% of the words and 12% of the phonemes were identified correctly o Control = 3% of the words and 13% of the phonemes were identified correctly Communication mode: It was necessary to use fingerspelling in conjunction with speech to effectively communicate. Patient also had progressive visual loss, so he could see only in one quadrant of his visual field. Speech Perception Scores:	Pure-tone audiometry: Patient: Unaided PTA average: 97dB Control: Mean Unaided PTA average: 103dB 6 Months Speech perception scores: • Minimal Pairs Test o Patient: mean closed-set vowel recognition score = 72% 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

Table 5. Audiological outcomes (Continued)

Study	Preoperative data	Postoperative data	Overall benefit (subjective assessment)	Follow-up
		o Control: mean closed-set consonant recognition score = 93% • Open-set word recognition (PBK): o Patient: 4% of the words and 20% of the phonemes were identified correctly o Control: 39% of the words and 61% of the phonemes were identified correctly		
Frewin et al. (2013)	Pure-tone audiometry: R. Thresholds: 500Hz-60dB, 1kHz-60dB, 2kHz-30dB, 4kHz-35dB, 6kHz-50dB, 8kHz-35dB L. Thresholds: 500Hz-60dB, 1kHz-60dB, 2kHz-35Hz, 4kHz-35dB, 6kHz-40dB, 8kHz-35dB Speech perception scores: • BKB sentences at 70 dBA in an auditory alone condition: 11% • BKB after a 4-week trial of consistent hearing aid use = 0%. Communication mode: Functional communication was severely impaired. Visual impairment confounded this, as traditional lip-reading cues were unavailable to supplement the auditory input. Manual signaling and Braille were also impaired due to hand contraction. Speech production was effortful. There was a delay in initiating speech, and intelligibility was affected at a supra-segmental level.	2 Months of right-sided implant use: Pure-tone audiometry: R. Thresholds: 500Hz-30dB, 1kHz-30dB, 2kHz-20dB, 4kHz-20dB, 6kHz-20dB L. Thresholds: 500Hz-30dB, 1kHz-30dB, 2kHz-25Hz, 4kHz-20dB, 6kHz-25dB Speech perception scores: • BKB sentences at 70 dBA under original conditions: using the CI with the contralateral ear occluded, the patient scored 66% keywords correct. With the contralateral ear open, she obtained 70%. 2 months of bilateral CI use (10 months since unilateral CI) Speech perception scores: • BKB sentences at 70 dBA: 88% when listening bilaterally. The first CI remained dominant, with a score of 76% keywords correct, but the more newly established second implant also demonstrated significant benefit, with a score of 65% keywords correct. PROM: • EuroQol: Across the five domains of mobility, self-care, usual activities, anxiety and depression, and pain or discomfort, no improvement was demonstrated. • NCIQ: measured improvement across the three domains of physical, psychological, and social between the CI-pre and CI-post conditions. Major improvement was noted on the social domain. Other: Localization testing was also performed using the York Crescent of Sound. A five-speaker array was chosen with a 30° separation. When bilaterally aided, her mean error of localization was 28°.	Significant Benefit	2-10m

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; NR: Not Reported/Not specified; NVA: Nederlandse vereniging voor audiologie test; PBK: Phonetically Balanced Kindergarten Test; PROM: Patient Reported Outcome Measures; SDS: Speech Discrimination Score; SNHL: sensory neural hearing loss; T-CAMP: Turkish version of the Clinical Assessment of Music Perception Test.

strated 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.[30] 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[25–27,33]. Sinnathuray 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 Sinnathuray 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.[30] (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[30,31]. These differences of earlier intervention could explain why limited benefit was achieved by the patients in the study by Sinnathuray et al.[35].

The other patient who had no observed benefit from CI was from the study by Santarelli et al.[35] 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 onCI 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.[3] 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.[39], 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[40]. 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[41]. However, bridging these preclinical trials to humans is going to take a long time, with estimates of around 20 years[42].

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.[34] 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.[43], 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.

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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