Indicators for Cochlear Implantation in Children with Auditory Neuropathy Spectrum Disorder: A Systematic Review

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CERTIFICATE

This is to certify that this dissertation entitled '**Indicators for Cochlear Implantation in Children with Auditory Neuropathy Spectrum Disorder: A Systematic Review'** is a bonafide work submitted as a part for the fulfillment for the degree of Master of Science (Audiology) of the student with Registration Number: 19AUD004. This has been carried out under the guidance of the faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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CERTIFICATE

This is to certify that this dissertation entitled "**Indicators for Cochlear Implantation in Children with Auditory Neuropathy Spectrum Disorder: A Systematic Review**" has been prepared under my supervision and guidance. It is also being certified that this dissertation has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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DECLARATION

This is to certify that this dissertation entitled "**Indicators for Cochlear Implantation in Children with Auditory Neuropathy Spectrum Disorder: A Systematic Review**" is the result of my study under the guidance of Dr. Prashanth Prabhu, Assistant Professor in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysore and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysore **Registration No:19AUD004**

September 2021

Dedicated to Mommy, Papa

&

To the beautiful city of Mysuru

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Your growth depends on what kind of environment you're exposed to .If it is nourishing, you'll bloom.

My journey from Varanasi to Mumbai and finally to Mysuru has been full of ups and downs. I have failed, learnt and succeeded. Few people have left a permanent mark in my life. Let's take a quick recap to appreciate them.

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Abstract

ANSD refers to a group of auditory diseases demonstrating intact outer hair cells and desynchronized neural firings of the auditory nerve.Cochlear implant has emerged as a promising intervention strategy for severe to profound sensorineaural hearing loss (SNHL).However,due to its variable outcomes in children with ANSD,a consensus has yet to be reached on its performance in them. This review aims to summarize and synthesize current evidence of the performance of CI in children with ANSD by identifying test tools that will predict post CI performance.A review of 17 articles was conducted in order to highlight these predictors.Most of the selected studies included case reports,case series,cohorts and comparison between children with ANSD and SNHL. Assessment of study quality reported overall low risk of bias.A set of pre operative and post operative indicators were identified that not only predicted speech and auditory performance but also gave some insight about site of lesion in ANSD individuals. This review also highlights the need to include more precise tools to describe the site of lesion in order to choose the most appropriate management strategy for children with ANSD.

Key Words: Auditory neuropathy spectrum disorder; cochlear implantation; children with ANSD; indicators;prognosis;systematic review

Chapter 1

Introduction

The term auditory neuropathy spectrum disorder (ANSD) is an expansion from auditory neuropathy (AN). It refers to a group of auditory diseases demonstrating intact outer hair cells and desynchronized neural firings of the auditory nerve (Starr et al., 1996). A wide range of localization of the sites of impaired functioning, ranging from the area of inner hair cells (IHCs) synapses to the auditory neural fibres has been explored using genetics and molecular biology experiments on animal models (Berlin et al., 2010; Moser et al., 2016; Shearer & Hansen, 2019). ANSD is a type of hearing loss demonstrated by the presence of Otoacoustic Emissions (OAEs) and/or measurable Cochlear Microphonics (CM) with no synchronous neural activity seen on auditory evoked brainstem response testing demonstrated by absent brainstem auditory evoked response (Walton et al., 2008). On Pure Tone Audiometry, the levels of pure tone thresholds range from normal hearing sensitivity to a profound degree (Berlin et al., 2010; Rance et al., 1999).

The underlying cause of ANSD may be congenital or acquired. Although previously believed to be very rare, studies show ANSD is very much prevalent.The pathophysiology of the disorder includes presynaptic (inner hair cell disorders), postsynaptic (disorders affecting the auditory ganglion, dendrites, and axons), and central (auditory brainstem) disorders (Rance & Starr, 2015). The task of rehabilitating ANSD patients has been very challenging. Current rehabilitative options for ANSD include hearing aids, a Frequency modulation(FM) system, and cochlear implants. The benefits of various rehabilitative measures for ANSD are variable and still being studied (Feirn et al., 2013).

A cochlear implant helps in establishing neural synchrony and improving hearing outcomes in patients with sensorineural hearing loss by directly stimulating the spiral ganglion cells of the auditory system and partially replacing the functions of hair cells (Buss et al., 2002; Hood et al., 2003; Mason et al., 2003; Shallop et al., 2001; Vermeire et al., 2003). When it comes to CI, reports show a variable (Teagle et al., 2010) but encouraging results (Breneman et al., 2012; Budenz et al., 2013; Walton et al., 2008). More so over, due to various sites of lesion involved, CI in ANSD has been an arguable issue.. If the lesion site lies in the cochlea, then bypassing the inner hair cells while directly stimulating the vestibulocochlear nerve should produce promising results. However, if the lesion site lies in the nerve itself, the chances of encountering similar limitations as seen in acoustic stimulation via hearing aids become greater (Sampaio et al., 2011).

Drawing a logical inference that those ANSD cases that receive some kind of benefit from hearing aids would certainly benefit better from cochlear implants, as it suggests that the nerve has some kind of functionality. Hence, ruling out the site of lesion before cochlear implantation gives an estimate of the prognosis of speech and hearing development in children with ANSD . With this background, we plan to conduct a review to list out a set of clinical diagnostic indicators that would help us to select successful ANSD candidates for cochlear implantation.

1.1 Prevalence

Initially, ANSD was believed to be of rare occurrence. However, the frequency of ANSD has been reported to be more than previously believed. The prevalence of ANSD is estimated to range between 0.23% and 0.94% in infants "at-risk" for hearing impairment (Foerst et al., 2006; Rance et al., 1999), whereas in another study that involved neonatal intensive care unit graduates, an ever-higher

prevalence of 1.96% was reported (Psarommatis et al., 1997). The prevalence reaches 7%, or even 11% amongst children with confirmed diagnosis of permanent hearing loss (Foerst et al., 2006; Rance, 2005; Rance et al., 1999).

1.2 Etiology

There are various underlying causes of ANSD. It could be congenital or acquired. Genetic abnormalities, perinatal asphyxia, or hyperbilirubinemia are some of the congenital causes. A dialogue on the auditory neurotoxic effects of hyperbilirubin on hearing has been published (Shapiro & Nakamura, 2001).Variants of ANSD also exist as specific genes or chromosome locations have been identified in some cases (Butinar et al., 1999). The largest proportion of ANSD is due to genetic factors. Thus, ANSD can be classified as syndromic, non-syndromic, or mitochondrial related(Manchaiah et al., 2011). Isolated genetic causes of ANSD are also frequently described due to mutations in the following genes- DFNB9, DFNB59, and AUNA1 , each one resulting into faulty protein-coding (Del Castillo & Del Castillo, 2012).

Acquired causes of ANSD include infections, demyelination disorders and vascular causes(Starr et al., 2000). An extended neonatal intensive care unit (NICU) stay is the most important perinatal risk factor for acquired ANSD (Teagle et al., 2010).ANSD, which occurs during late childhood or adulthood and could be associated with peripheral neuropathies. These peripheral neuropathies could be a result of genetic abnormalities or some other disease process. For example, Charcot–Marie–Tooth disease affects both motor and sensory nerves. Subtypes of Charcot–Marie–Tooth disease are associated with a demyelinating disease or axonal peripheral neuropathies, both of which affect the auditory nerve (Rance et al., 2012). The age of onset for Charcot-Marie-Tooth can vary. Friedreich's ataxia, on the other

hand, has an adult-onset. It is an inherited polyneuropathy disease that affects the VIIIth nerve. Other such neuropathies are Epstein–Barr virus, Guillain–Barr syndrome, etc. Degeneration of the auditory nerve occurs due to disease processes such as mumps in unilateral cases of late–acquired ANSD (Liu et al., 2012). Likewise, risk factors are also diverse.

1.3 Pathophysiology

ANSD leads to impaired neural auditory function due to loss of synchrony of in auditory nerves (Rance, 2005). The site for this dys-synchrony can be localized to the following- terminals of dendrites of the auditory nerve, axon of nerve fibres , ganglion cells (Rance & Starr, 2015; Starr et al., 1996), the inner hair cells of the cochlea and ribbon synapse (Amatuzzi et al., 2001; Harrison, 1998; Liberman et al., 2006). The commonest cause of the dys-synchrony is believed to be irregular or absent inner hair calls(IHCs) in the presence of outer hair cells(OHCs) (Gibson & Graham, 2008; Walton et al., 2008) because it affects the tuning within the cochlea. Site of lesion at the brainstem level is also mentioned in the literature(Attias et al., 2012). Clients with abnormal brainstem responses can have good speech perception in quiet due to the absence of lesions in the cortical region(Narne et al., 2014). The presence of varied sites of lesion leads to different types of hearing loss, which gave way to the adoption of the term "auditory neuropathy spectrum disorder" (Hayes & Sininger, 2008).

ANSD may be unilateral or bilateral, permanent or transient, stable or fluctuating, or progressive(Ćeranić & Luxon, 2004; C. Liu et al., 2012). Sudden-onset ANSD has been very recently reported .It can be the earliest sign of undetected Brown-Vialetto-Van Laere (BVVL) syndrome arising due to riboflavin transporter deficiency (Gedik Soyuyuce et al., 2021). Dysfunction in ANSD can exist at several

sites. These sites include OHC, IHC, VIIIth nerve, and pre-and postganglionic nerve fibers as well as their mosaic pattern of functioning (Berlin et al., 2010).

1.4 Diagnosis

Individuals diagnosed with ANSD show integrity of OHCs but abnormal pathways beyond the OHC and up to and including the VIIIth nerve. Evidence of pathology beyond the OHCs includes an abnormal or absent ABR in the presence of OAE and /or CM. It is important to ensure those cases with absent OAE and present CM that this response is not a result of the good low-frequency hearing. A 500-Hz toneburst stimulus could be used to assess low-frequency hearing sensitivity. Use of 1-kHz tone pip for assessing the same is recommended by the United Kingdom's NHS NHSP (2011) guidelines.

As mentioned dysfunction can exist at many sites. A mosaic pattern of functioning at different sites like IHC, OHC also subsists (Berlin et al., 2010).Absent OAEs upon retest acts as evidence to the mosaic pattern of functioning (Starr et al., 2008). Circulatory issues and channel disruption are mechanisms responsible for regression in OAEs. Cochlear microphonics have a greater advantage in terms of not getting affected, as does OAE, owing to its dual source of generation of both IHC and OHCs. Another reason could be differences in populations of OHCs in different frequency regions.

Although the integrity of OHC can be assessed with OAE, audiological tools cannot identify the exact site of dysfunction. In fact, absent or elevated responses were found in middle ear reflexes in the majority of individuals with ANSD (Berlin et al., 2005). The ABR is an objective measure of neural activation and neural synchrony and not a test of hearing. There is a close association between frequency-specific ABR thresholds and behavioral thresholds in hearing loss cases

(Gorga et al., 2006). However, in individuals with disturbed synchrony, absent or abnormal ABR is associated with a range of pure tone thresholds ranging from normal hearing to profound hearing loss (Berlin et al., 2010). Currently, no audiology tools can fully differentiate the site of lesion beyond the OHCs. Thus fully isolating a sensory Inner Hair Cell loss from axonal loss or dys-synchrony due to demyelination still poses a challenge.

1.5 Management

Literature reveals that many hurdles exist in the treatment and rehabilitation of ANSD. Medication and acoustic amplification have played limited roles in terms of benefits, according to the currently available clinical evidence (Roush et al., 2011; Starr et al., 2008). In fact, the early attempts with CI to treat hearing loss in ANSD weren't a success either (Roush et al., 2011). The common CI contraindications in ANSD included nerve degeneration secondary to processes like demyelination and axon impairment(Starr et al., 1996) , conduction blockage, and absence of excitability of the auditory nerve fibers (Starr et al. 2003). This was supported by reports of the limited efficacy of cochlear implantation in patients with ANSD in the very initial attempts(Miyamoto et al., 1999; Trautwein et al., 2000). However, later reports on CI in children with ANSD have shown a variable (Teagle et al., 2010) but more encouraging outcomes (Breneman et al., 2012; Budenz et al., 2013; Walton et al., 2008). The variable results were attributed to the wide range of lesion sites.

Although excellent restoration of auditory functions and speech and language development is attributed to early implantation, the decision to undertake cochlear implantation at an early age is complicated by the spontaneous improvement of auditory phenotypes observed in approximately 20% of children with ANSD (Harrison et al., 2015). There is much debate concerning the benefits of

CI in children with ANSD due to its unexplored physiology. However, evidence obtained from animal experiments have shown how synchronization is restored through electrical stimulation with CI(Zhou et al., 1995).

Electrical stimulation could bypass the lesion site and restore auditory functions, if the affected site was presynaptic and implantation was done at an early age, much like the patients with typical SNHL. Many differences exist between ANSD and SNHL in terms of lesion site and cochlear function. These differences may affect the auditory pathway in receiving, transmitting, and processing complex electrical signals. Thus, clinical diagnostic indicators must be highlighted that can help to target children who will benefit from CI.

1.6 Need for the study

ANSD includes a heterogeneous population that varies with aetiologies and sites of lesion. It is evident that the exact sites of the lesion in ANSD determine outcomes with CI. That is, presynaptic lesions, which are located in the membranous labyrinth, are associated with good CI performance, while the postsynaptic lesions in the auditory nerve are not (Eppsteiner et al., 2012). Genetic defects which are now known to be a proven cause of ANSD, amongst which mutations in the OTOF gene were found out to be the most common cause of congenital auditory neuropathy (Loundon et al., 2005; Rodríguez-Ballesteros et al., 2003; Rouillon et al., 2006; Wu et al., 2011). There is a reduction of synaptic vesicle exocytosis at ribbon synapse due to mutations in the OTOF gene (Michalski et al., 2017; Pangšrič et al., 2010). As the site of lesion is presynaptic, CI performance in these individuals has reported good benefits (Zheng & Liu, 2020).Outcomes of CI in postsynaptic ANSD show variable benefits from the baseline (Chaudhry et al., 2020).

Due to the inconstancies surrounding the benefits of CI in children with ANSD, there is a need to identify these children at an early stage so that a timely rehabilitative approach can be taken up to reach maximum potential in terms of speech and language development. Audiological and electrophysiological measures such as behavioral audiometry, speech recognition scores, Otoacoustic Emissions, Auditory Brainstem Responses, Acoustic Immittance, and Cortical Auditory Evoked Potentials help in the identification of ANSD .Other diagnostic tools such as round window electrocochleography help in the identification of subtypes of ANSD (McMahon et al., 2008). As there is a lot of research carried out on CI in ANSD, there is a need to collect and synthesize available literature. There is a necessity to pool this data in order to generate more reliable estimations of cochlear implant efficacy. Moreover, it'll aid in improved patient selection for CI along with improved counseling and management.

1.7 Aim of the study

The aim of this review is to identify indicators for cochlear implantation in children with ANSD to predict the outcomes of auditory and speech performance in order to select suitable CI candidates.

1.8 Objectives of the study

- To select articles based on the aim of the study that also meets the inclusion and exclusion criteria.
- To report the outcome of cochlear implants in these children, if mentioned.
- To identify pre-operative and postoperative prognostic indicators for CI in children with ANSD.

Chapter 2

Methods

A review of the literature was conducted using several search parameters. Inclusion exclusion criteria were set. Possible keywords, related search words, and their derivatives relevant to the research question were developed and selected. The databases which were used to search included Google Scholar, MEDLINE, AJOL [African Journals Online], Science Direct, and PubMed. The keywords included auditory neuropathy, ANSD, auditory dys-synchrony, children, and cochlear implants. The review was carried out using PRISMA guidelines (Moher et al., 2009). Eligibility criteria included articles published in peer-reviewed journals, primary reports on cochlear implantation in children with ANSD up to 12 years of age, and articles published in the English language were considered. Articles based on animal models, histopathological studies, pharmacological models, articles with insufficient data, and studies with duplicated data were excluded. Those children having cochlear anomalies, associated syndromes, or multiple disabilities weren't considered for the study. A systematic search was conducted using the above-mentioned electronic databases to obtain English language articles published in peer-reviewed journals for data extraction. The search strategy consisted of a comprehensive list of search terms to identify relevant articles. This was followed by the title and abstract screening using the inclusion and exclusion criteria. All eligible articles' full texts were obtained and reviewed to assess eligibility, as per the criteria. A manual search was also done to identify known articles. Disagreements at the screening stage between the reviewers were restored through discussion. The reviewers then extracted relevant data suggested by the PRISMA-P from the studies

selected for inclusion and appraised each study according to the pre-defined risk of bias assessment protocols.

The extracted information included authors' names, type of research design, type of study population and their number, methodology, participant demographics, specific factors that can exclude implantation, evaluations and etiological factors, the outcome of the study, and its merits and demerits.

In total, 9630 articles, with or without abstracts, were identified in all databases. In a pre-selection of these citations, based on reading the titles and abstracts of all studies found in the electronic search, 239 were excluded due to: repetition, 8760; excluded by title screening, 604; excluded by abstract screening. For complete reading, 27 articles were selected. After reading the 27 texts, ten articles were excluded due to: studies in which the population's age did not fit the selection criteria, three; studies that involved children with associated comorbid conditions, three; and studies which were review articles, four. In the end, 17 articles met the inclusion criteria. The details of the above are provided in the PRISMA table shown in Figure 2.1.

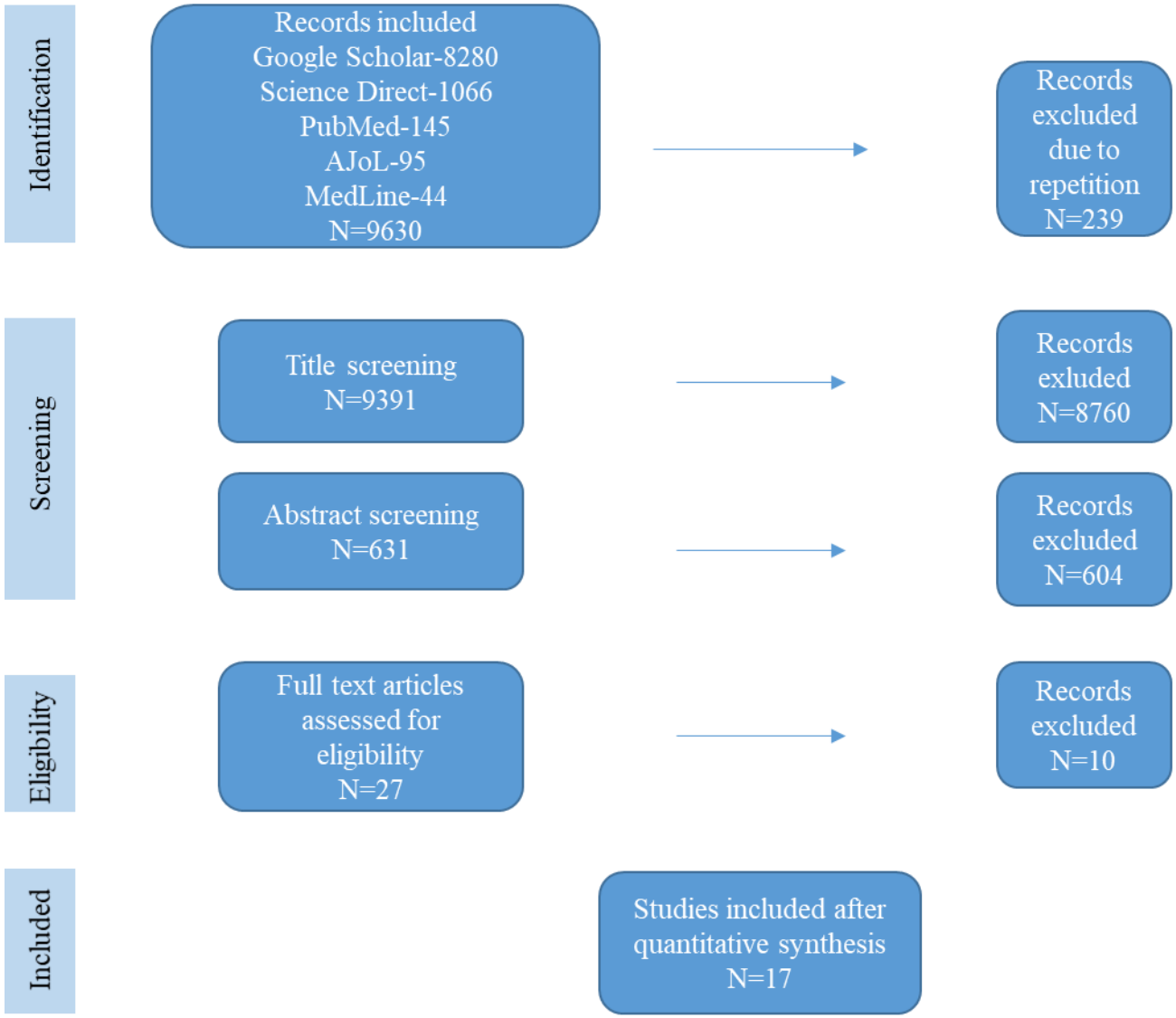

Figure 2.1 Flowchart depicting selection process of articles in the systematic review

Chapter 3

Results

3.1 Selection of studies

The application of the initial search strategy and the inclusion and exclusion criteria provided 17 papers for quality appraisal and synthesis. In total, 9630 articles, with or without abstracts, were identified in all the databases. In a pre-selection of these citations, based on reading the titles and abstracts of all studies found in the electronic search, 509 were excluded due to: repetition, 8760; excluded by title screening, 334; excluded by abstract screening. For complete reading, 27 articles were selected. After reading the 27 texts, ten articles were excluded due to: studies in which the population's age did not fit the selection criteria, one; studies that involved children with associated comorbid conditions, five; studies which were review articles, four.

In the end, 17 articles met the inclusion criteria. All the studies were retrospective in design except one. Of those studies included in this review, ten were comparative, two were case reports, two were cohort studies, and three were case series.

3.2 Summary of data extraction

Data extraction from all the selected articles was carried out and classified using the following criteria-Author and year of publication, research design, research question, type of population, method, outcome, and discussion. The data extraction sheet reveals that studies included were published in the time range of 2000 to 2018. Selected studies mainly consisted of comparative studies, case reports, case series, and cohorts in design. The largest of these studies reported the results of 136 children(Daneshi et al., 2018). All

subjects included in the study were diagnosed with ANSD, out of which few were selected to undergo cochlear implantation. Different kinds of pre-operative, intra operative and postoperative tests were conducted on the subjects to find out the prognosis for cochlear implantation in ANSD children and compare speech perception outcomes with SNHL children.

The majorly used pre-operative tests were electrophysiological tests and radiological tests. Intraoperative tests consisted of measuring ECAP using Neural Response Telemetry or Neural response Imaging. Auditory performance and Speech perception tests were assessed after switch on at different follow-up intervals using a variety of materials such as Categories of Auditory Performance (CAP), Speech Intelligibility Rate (SIR), Meaningful Auditory Integration Scale (MAIS), Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS), Early speech perception(ESP), Mandarin Early Speech Perception (MESP) test, etc. Electrophysiological tests like EABR were also done to determine speech perception results.

Speech recognition outcomes in implanted children with ANSD vs. implanted children with SNHL was portrayed in six studies (Attias et al., 2017; Jeon et al., 2013; Jeong et al., 2007; Runge-Samuelson et al., 2008; Sarankumar et al., 2018; Trautwein et al., 2000). Most of them showed no significant difference in the performance of the two groups-ANSD and cochlear hearing loss with no neural pathology, indicating similar performance in the two groups.

Subjects with GJB2 mutations and SLC26A4 mutations were included for comparison with subjects with OTOF mutations(Wu et al., 2018).EABR waveforms were compared in ANSD and normal-hearing groups (McMahon et al., 2008). Different Prognostic indicators identified in all the studies through this review have been grouped under eight tables.

Table 3.21 Showing data extraction of experience with a hearing aid as a prognostic indicator.

Author (Year)	Research design	Research question	Population type	Method	Outcome	Discussion
Trautwein et al., 2000	Case report	Cochlear implantation of ANSD	An 18-month-old boy with ANSD compared with a set of 10 children with cochlear hearing loss	Hearing aid experience 3 months followed by one-sided cochlear implantation.	One-year postimplantation, the child with AN could discriminate the sounds like most of the children with SNHL.Improvement in ESP category also.	1.Diagnosis of AN shouldn't be an immediate referral.2.Trial with a hearing aid is a necessity
Fei et al., 2011	Case report	To report outcomes and preliminary clinical evidence of the efficacy of CI in ANSD patients	4-year-old boy with ANSD	MESP, MAIS, CAP and SIR were used to assess the benefits from CI. The tests were administered before surgery and at 3 months and 7 months after switch on	The child has benefit from CI in both hearing sensitivity and speech recognition performance after a period of 7 months of using the CI	The decision to implant depends on experience of using hearing aids in both ears which help to reach a relatively high level of aided hearing sensitivity

Sinha, 2015	Retrospective study	What would be more beneficial to children with ANSD? Hearing aids or Cochlear Implant	65 cases -42 bilateral ANSD were included	Bilateral fitting of hearing aids for 6 months. Increase in CAP score by 1(intermediate benefit) then only child will be sent for CI.	Only 13 were selected for CI who showed "good" progress on CAP after six months.	Hearing aid trial and its benefit should be explored before conducting CI in ANSD individuals. Those who derive "intermediate benefit" from hearing aid should certainly undergo CI

Table 3.21 shows how performance with a hearing aid prior to cochlear implantation plays a role not only in the decision-making process for Cochlear Implantation but also on the auditory and speech-language performance of an individual.

Table 3.22 Showing Age at the time of cochlear implantation as a prognostic indicator.

Author (Year)	Research design	Research question	Population type	Method	Outcome	Discussion
Daneshi et al., 2018	Retrospective multicenter study	What is the effect of age at the time of implantation	136 children included; Group1-includes those having age of implant less than 24 months, Group 2-those having age of implant more than 24 months of age	Auditory performance by CAP and speech production assessment by SIR scores to be determined pre and postoperatively	The median CAP and SIR score during the second year after surgery was significantly better in children lesser than 24 months of age	Performance with CI in terms of audition and speech production skills depends on age at the time of implantation and the duration of post-implant follow-up.
Liu et al., 2014	Case series	To evaluate the auditory and speech abilities in children with ANSD after CI and determine the role of age at implantation.	Ten children with ANSD participated in this retrospective case series study.	Two groups: first;age at the time of implant less than 24 months and second who underwent after 24 months of age. Their auditory and speech abilities were evaluated using different tests.	Scores of children with ANSD who received CI before 24 months tended to be better than those of children who received CI after 24 months.	Early intervention such as that of CI before the age of 24 months leads to better acquisition of auditory and speech skills even in children with ANSD

This table highlights how children with ANSD implanted with CI less than the age of 24 months showed better performance in the longer run.

Table 3.23 Shows studies with EABR data.

Author (Year)	Research design	Research question	Population type	Method	Outcome	Discussion
Runge-Samuelson et al., 2008	Retrospective study	Quantitative analysis of EABR in implanted children with and without ANSD	Five children with confirmed congenital ANSD and 27 children with SNHL	Intraoperative EABR wave V threshold, suprathreshold amplitude, and latency measures were compared between groups.	Wide range of EABR thresholds & amplitudes regardless of etiology.Relative to the averaged data of children with SNHL, subjects with ANSD showed an average or below-average EABR thresholds, and suprathreshold amplitudes.	Sensitivity to electric stimulation in ANSD group is comparable to or better than the SNHL group. Reduced synchronous activity across and within fibres evident via EABR waveform Range of EABR responses reflects the variety of ANSD etiologies and severity.

Jeon et al., 2013	Retrospective study	To analyze the pattern of EABR in ANSD patients and to compare their performances with controls.	Eleven patients with ANSD and nine control subjects with SNHL without neural pathology	EABR threshold, amplitude, and Wave V latency were analyzed as the EABR parameters. Speech perception ability was assessed by using the CAP score & IT- MAIS.	All controls responded to EABR except 6. The EABR threshold of ANSD patients was equivalent to that of disease controls. However, the Wave V latency displayed variable lengths, and the amplitude showed a wider distribution compared to disease controls.	EABR results may provide some indication about future performance. However, they can't be a very reliable indicator as patients with absent EABR also reached good performance levels.

From the studies included in Table 3.23, it is clear that the presence of EABR is not a strict predictor of how good the prognosis with a cochlear implant could be. In certain cases of ANSD, children with absent EABR responses have also achieved a comparable performance in children with present EABR. But EABR results can help establish realistic expectations about future performance.

Table 3.24 Depicts a study regarding finding the site of lesion in neural pathology.

Author (Year)	Research design	Research question	Population type	Method	Outcome	Discussion
McMohan et al.,2008	Retrospective Study	Does Frequency specific electrocochleography indicates that presynaptic and post synaptic mechanisms of auditory neuropathy exist	14 subjects with ANSD compared with responses from two normally hearing subjects	Intra op sound evoked round window EcochG and EABR done.	Two dominant ECochG waveforms identified in ANSD group: (a)waveform showing a prolonged summating Potential(SP) latency (b)waveform showing a normal latency SP followed by DP. Three types of EABR were observed: a normal EABR waveform , showing waves II–V; an EABR waveform showing poor	subjects with delayed latency SP showed good EABR waveforms, consistent with a presynaptic lesion.Subjects who showed ECochG waveforms with a normal latency SP and a Dendritic Potential showed poor or absent EABR waveforms consistent with a postsynaptic disruption.

					waveform for wave V ; or an absent EABR waveform.	

In all the subjects who showed a Summating Potential(SP) and Dendritic Potential(DP), the resultant EABR waveform was either absent or showed poor waveform morphology. On the other hand, for seven of eight subjects who showed a prolonged latency SP waveform with or without residual CAP activity, the EABR appeared normal. The results of this study demonstrate that in those ears where there was no obvious DP, the latency of the SP waveform was significantly delayed, where the mean latency was 1.35 msec, whereas, in those subjects where the DP was present, the mean latency of the SP was 0.71 msec.

Table 3.25 Radiological information as a pre operative indicator.

Author (year)	Research design	Research question	Population type	Method	Outcome	Discussion
Jeong , 2013	Retrospective study	To assess if radiologic studies and electrophysiologic tests can predict speech perception abilities post CI in ANSD individuals	Fifteen children with ANSD	MRI and CT were used.ESRT, EABR, and ECAP performed. Post CI , speech perception abilities also measured	Normal BCNC and normal cochlear nerve in children with ANSD showed excellent speech perception abilities after CI.	Pre-operative radiologic studies along with Early postoperative electrophysiologic tests, like ESR and ECAP, were reliable predictors of speech perception abilities after CI. EABR –as a predictor was inconclusive.

Additionally, In the Electrical stapedial reflex (ESR) test, all the tested electrodes in the good performers' group showed a robust response, with mean thresholds of 217 current levels. Whereas the poor performers' group showed no response. A similar response pattern was observed from both the groups on ECAP tests. Incidence and thresholds of ESR and ECAP showed a significant difference between the two groups ($p < 0.001$, Mann–Whitney U test). In contrast, the mean thresholds of implant-EABR were not significantly different between the groups.

Table 3.26 Includes post operative indicators like ECAP.

Author (year)	Research design	Research question	Population type	Method	Outcome	Discussion
Shallop et al.,2001	Case series	CI in 5 cases of auditory neuropathy:postoperative findings and progress	Five children in the age range of 5 to 76 months	Intraoperative testing included verification of cochlear implant function, visually detected electrical stapedius reflexes (VESR), and NRT measures on at least four electrodes.	All children showed significant improvement in SAT/SRT and ESP results. All of the five children had good intraoperative NRT results.Majority also had good postoperative EABR results	The pre-operative dyschronous auditory brainstem neural potentials are apparently restored to some degree in five cases as shown by the clear presence of N1 in the NRT results and waves II–V in the EABR results
Shallop et al., 2005	Case series	Characteristics of electrically evoked potentials in patients with ANSD	2 children	Pre op(operation), intra op and post op evoked potentials .NRT and NRI done intra op and post op. EABR post op	Absent preop evoked potential, NRT showed excellent neural synchrony intra op	Pre op ,intra op, post op, evoked potentials reveal restoration of neural synchrony at multiple levels of auditory pathway with CI and rehabilitation.

Jeong et al., 2007	Retrospective study	To assess the status of auditory nerve in patients with ANSD and to assess the outcomes of CI in them	9 ANSD children with SNHL matched controls on certain variables	Comparison of slopes of ECAP amplitude growth functions of children with ANSD with those of control subjects, screening test for OTOF gene mutation to exclude endocochlear lesion. ECAP was measured using the NRT. Performance outcome measured using CAP,MW & common phrase test	Mutations in OTOF gene were identified in one patient. EABR recorded 3 weeks post op. There was no significant difference between the two groups in terms of growth function of ECAP amplitude and speech perception abilities	Spiral ganglion cell population of children with ANSD could be comparable to that of children with sensorineural hearing loss. The NRT system is superior to the EABR-recording system in terms of ECAP measurement(direct measurement and no muscle artifact)

Carvalho et al., 2011	Prospective cohort cross-sectional study	To evaluate the auditory performance and the characteristics of the ECAP in CI for 6 months. ECAP threshold measurements were taken at the 80 and 35Hz stimulation frequencies.	18 children with ANSD	Evaluation of auditory perception is done by sound field measurement and speech perception tests	No significant statistical difference in the development of auditory Skills or in the ECAP's characteristics at 80 Hz and 35Hz stimulation rate. .	The efficacy of implantation in ANSD children can be measured using-difference in speech recognition performance after implantation compared to SNHL,pre vs post implant scores,hearing threshold improvement using CI,presence of EABR waveforms
Fei Ji et al .,2014	Retrospective study	To study the characteristics of NRT in AN patients who had received cochlear implants	seven ANSD patients with Twenty-one CI implantees with SNHL as the control group	The incidence of ECAPs, threshold of wave N1, and amplitude of N1-P2 in the AN group were analyzed and compared between the two groups.	The intraoperative incidence of valid ECAPs in the AN group was 42.9%, and the postoperative incidence was 66.7%, both lower than the SNHL group, which were 95.2% and 100%, respectively.	The lower differentiation in ECAP of ANSD group reflected loss in spiral ganglions, number excited neurons, and the lower degree of auditory nerve synchronization. ECAPs could be an indicator of successful hearing reconstruction, but a long-term observation is required between ECAP

						and postoperative hearing and speech performance.

The presence of valid ECAP waveforms usually signifies activation of electrodes and good response of neurons to electrical stimuli. This could act as an objective indicator of hearing reconstruction. Thus ECAP has a significant correlation with postoperative hearing and speech performance.

Table 3.27 Studies comparing speech perception outcomes only.

Author (year)	Research design	Research question	Population type	Method	Outcome	Discussion
Attias et al 2017	Cohort study	Auditory performance and electrical stimulation measures in CI recipients with ANSD compared with severe-profound SNHL	16 patients with ANSD,16 with SNHL-control group	The main outcome measures were between-group differences in the following parameters: (1) Auditory and speech tests. (2) Residual hearing(3) Electrical stimulation parameters. (4) Correlations of residual hearing at low frequencies with electrical thresholds at the basal, middle, and apical electrodes	No significant difference in auditory and speech recognition tests in quiet or noisy conditions. More children in the ANSD than the SNHL group attended mainstream educational settings, the difference was not statistically significant. Mean tNRT levels recorded from the seven basal electrodes and the seven apical electrodes were significantly lower in the ANSD than SNHL Group.The children with ANSD had more residual hearing before and after implantation	Direct implication in cochlear implant mapping in children with residual hearing, and especially those with isolated ANSD who requires less current discharge for hearing perception.
Sarankumar et al 2018	Retrospective Study	To compare the outcomes of CI in children with	Ten patients with ANSD	Auditory and speech scores were compared between baseline	Significant benefits were seen compared to the baseline and one-year post CI. No	CI in children with ANSD has shown benefits comparable to children with

		ANSD and age-matched controls with profound SNHL, using CAP, SIR, MAIS, MUSS, and to determine the role of CAEP in benefit evaluation after CI.		and after 12 months of habilitation in children with ANSD.	significant difference in outcomes between the two groups. P1 wave of CAEP shows good correlation with subjective results.	SNHL. CAEP has proven to be a useful tool in objectively assessing cortical maturity in children with CI.

Table 3.28 Genetic testing in order to find out presence of OTOF mutations.

Author (year)	Research design	Age at CI	Population type	Method	Outcome	Discussion
Wu et al., 2018	Retrospective study	The age at which CI was performed ranged from 1.0 to 5.6 years.	The genotypes of 10 subjects with ANSD were confirmed by sequencing exons of OTOF gene. All patients received CI. Subjects with GJB2 mutations and SLC26A4 mutations were included for comparison.	ECAPs measured in patients receiving CI. CAP and SIR scores were assessed at different intervals after CI.	Serial behavioural audiometric testing revealed stable hearing levels. During surgery, all ten patients with OTOF mutations revealed robust ECAPs, which were comparable in both groups. No difference in CAP or SIR scores in both groups.	CI is a viable option for patients with OTOF mutations. It should be carried out in them whenever indicated, and at the earliest

The above study in Table 3.28 represents the largest series in the literature documenting data related to ANSD individuals with OTOF mutations. These results were cross-referred to patients with GJB2 or SLC26A4 mutations. Outcomes in ANSD patients with OTOF mutations were as favorable as those in CI recipients with a definite cochlear pathology.

3.3 Summary of quality assessment

Quality in prognostic studies tools was used to assess all the included studies except case reports and case series. QUIPS tool consisted of six domains –study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. The following criteria were used to classify the risk of bias-
if all domains were classified as having a low risk of bias, then the paper was classified as low risk of bias; if one or more domains were classified as having a high risk of bias or more than 3 moderate risk of bias, then the paper was classified as high risk of bias. All papers in between were classified as having a moderate risk of bias.

All of the studies included fell under low risk of bias. There were few domains labeled as NA, that are Not Applicable. Few studies were totally outcome-based and compared speech perception results.Thus, they have been excluded from the quality assessment of prognostic factors and labeled as NA (Attias et al., 2017; Runge-Samuelson et al., 2008; Sarankumar et al., 2018)

Table 3.31 Depicting a summary of quality assessment of all articles included in the review.

Author & Year	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting	Overall Rating
Runge et al ,2008	Low	Low	**NA**	Low	Low	Low	Low
McMohan et al, 2008	Low	Low	Low	Low	Low	Low	Low
Jeong et al, 2007	Low	Low	Low	Low	Low	Low	Low
Carvalho et al, 2011	Low	Low	Low	Low	Low	Low	Low
Jeong , 2013	Low	Low	Low	Low	Low	Low	Low
Jeon, 2013	Low	Low	Low	Low	Low	Low	Low
Fei Ji et al,2014	Low	Low	Low	Low	Low	Low	Low

Sinha, 2015	Low	Low	Low	Low	Low	Low	Low
Attias et al, 2017	Low	Low	**NA**	Low	Low	Low	Low
Wu et al, 2018	Low	Low	Low	Low	Low	Low	Low
Sarankumar et al 2018	Low	Low	**NA**	Low	Low	Low	Low
Daneshi et al ,2018	Low	Low	Low	Low	Low	Low	Low

Chapter 4

Discussion

The current review was carried out in order to identify the prognostic indicators that would assist in selecting eligible candidates for cochlear implantation in children with ANSD. These indicators will predict auditory and speech performance in children with ANSD using a cochlear implant. Highlighting such predictors can aid in improving the decision-making skills with respect to cochlear implantation in such children and further help in utilization of critical age period and initiation of timely rehabilitation with cochlear implantation. A total of 17 articles were identified and selected for the review.

Prognostic factors for indicating cochlear implant in children with ANSD were clearly defined in some studies. Age was taken up as an indicator to compare speech perception outcomes in children implanted before and after 24 months of age.It showed that cochlear implantation performed before the age of 24 months achieved greater speech perception scores during the longer follow-up duration (Daneshi et al., 2018; Y. Liu et al., 2014). Such outcomes support the recent trend that suggests early cochlear implantation in pre-lingually deaf children (May-Mederake, 2012). Nikolopoulos et al. (1999) also highlighted the importance of age at implantation in 126 children with prelingual deafness(Nikolopoulos et al., 1999). If implanted under one year of age, deaf children may also develop some pre-verbal communication behaviors compared to age-matched normally hearing children(Tait et al., 2007). Thus, these studies point towards receiving implants as early as possible to facilitate speech perception skills and speech intelligibility and maximize health gain from the intervention.

Serial behavioral audiometric testing revealed stable hearing levels in ANSD patients with OTOF mutations. Thus, cochlear implantation should be performed in patients with OTOF mutations whenever indicated(Wu et al., 2018). A very recent systematic review also highlights similar findings(Zheng & Liu, 2020). However, age alone should not be used as a criterion to decide implant candidacy. Genetic makeup, developmental and genetic comorbidities should also be considered. Considering the low risk of bias in the included studies, age emerges as a strong predictor for CI.

Even though the decision to fit a child with a cochlear implant is made on an individual case basis, a great value is to be obtained from sub-grouping sets of patients. This was reflected by the results of round-window ECochG that provided a classification of ANSD into presynaptic and postsynaptic. This above-mentioned study compares the types of EcochG waveforms, summating potential (SP) latency, and types of EABR waveforms. Presynaptic and postsynaptic mechanism of ANSD was supported by the round-window ECochG waveforms measured before implantation and the EABR waveforms measured after cochlear implantation (McMahon et al., 2008). That is, all those subjects who showed ECochG waveforms with a delayed latency of SP showed good EABR waveforms, very much in synchrony with a presynaptic lesion. In contrast, subjects with ECochG waveforms with a normal SP showed absent or very poor morphology of EABR waveforms after cochlear implantation. The absence of EABR waveforms point towards primary afferent neuron dysfunction and auditory brainstem disruption. This form of classification will facilitate clinical decision making and planning of health care services

Another prognostic factor to be highlighted is experience and exposure to hearing aids before cochlear implantation. There are various studies that focus on how rehabilitation with hearing aid before cochlear implantation plays a major role in enhancing speech, listening, and language outcomes (Fei et al., 2011; Sinha, 2015; Trautwein et al., 2000). Performance with a hearing aid was taken up as a prognostic indicator in one study where on the basis of the CAP scores, benefit with a hearing aid was classified into three categories-no benefit, intermediate benefit, and good benefit. All ANSD cases that derived "intermediate benefit" from hearing aid usage, that is, increase in CAP score by 1 in 6 months, were considered for unilateral cochlear implant(Sinha, 2015).This has also been conveyed in a study where those infants with prelingual deafness who had undergone a trial with hearing aids demonstrated a significant positive effect on auditory skills in comparison with infants without hearing aid trial (Chen et al., 2010). The low risk of bias associated with the included studies adds to the strength of this indicator.

In one of the studies, radiological tests such as MRI and CT were used to identify good candidates for a cochlear implant. Normal dimensions of the Bony Cochlear Nerve Canal (BCNC) and cochlear nerve were found to correlate with speech perception abilities after CI. Conversely, narrow or obliterated BCNC and a deficient cochlear nerve correlated with poor speech perception (Jeong & Kim, 2013). Pre-operative predictors like CT and MRI, were therefore found to be reliable prognostic indicators of CI. A similar finding has been reflected in a study by Wei and colleagues where the diameter of the Cochlear Nerve Canal and the number of nerve bundles significantly predict auditory outcomes for CI patients with Cochlear Nerve Deficiency. These results suggest how pre-surgical imaging can be useful in predicting CI outcomes (Wei et al., 2017). There has been a surge in

identifying tools in order to define site of lesion in ANSD cases. This fact has also been indicated by a study on Diffusion Magnet Resource Imaging. Such imaging techniques may supplement the existing battery of tests to characterize the site of lesion and extent of dysfunction in individuals with ANSD(Zanin et al., 2020) .

Studies included in the review also consist of early postoperative predictors of speech and auditory outcomes with a cochlear implant. One of them indicated that in patients with ANSD, waveforms of Neural Response Telemetry could be present with characteristics of low incidence, low differentiation, and large variation. However, the ECAP incidence in SNHL implantees was 95.2% and in the ANSD group was 42.9%, and the postoperative incidence was 66.7%, either of which was lower than for SNHL. Thus, Ji and colleagues suggested ECAP data can provide information about hearing reconstruction post cochlear implantation. However, the large variation in the ECAP responses calls for long-term observation in order to draw out concrete conclusions. (Ji et al., 2014). The correlation of ECAP with postoperative hearing and speech performance has also been supported by other studies (Guedes et al., 2007; Kim et al., 2010; Schvartz-Leyzac & Pfingst, 2018). ECAP, an early post-operative indicator, has a significant correlation with speech and hearing performance in children with ANSD (Kim et al., 2010). Another study included in the review reflected that almost all electrodes tested in the good performers' group showed evoked responses on ESR and ECAP tests, whereas no evoked response was observed in the poor performers' group. ESR and ECAP are, without exception, reliable predictors for postoperative speech perception abilities (Jeong & Kim, 2013). Intraoperative ESR and early postoperative ECAP could be used to predict long-term speech perception outcomes due to their ease of

administration as compared to EABR. Therefore, they may aid in choosing an appropriate habilitation method for each recipient early after CI.

On similar lines, all five children with ANSD showed good intraoperative NRT result(Shallop et al., 2001). On the contrary, there was no significant difference between the two groups of ANSD and SNHL in the slope of the ECAP amplitude growth function and speech perception abilities(Jeong et al., 2007). There are many important correlations between speech perception and parameters of ECAP recordings in the literature; however, reporting was equivocal. Thus, this reduces the strength of ECAP as a predictor of speech perception. More research is needed to further investigate and probe in order to conclude ECAP as a predictor (van Eijl et al., 2017).

In another study, all controls consisting of children with SNHL responded to EABR, whereas few ANSD patients did not show any response. The nonresponse group demonstrated variable outcomes with cochlear implants, although they still benefited from CI (Jeong & Kim, 2013). Another study included in the review quantified characteristics of EABR waveforms of children with ANSD and SNHL. It highlighted the relationship between wave V thresholds of the EABR and auditory and speech outcomes in pediatric cochlear implant recipients(Runge-Samuelson et al., 2008). Thus, all these studies call attention to the role of EABR as a predictor of CI performance. This is further supported by a study that shows how EABR, when combined with MRI, can help immediately predict CI outcomes in children with Cochlear nerve deficiency(Yamazaki et al., 2015).

Thus, the current review helped us to identify various pre-operative and postoperative indicators that would strengthen the decision-making skills for cochlear implantation in children with ANSD. Pre-operative indicators consisted of

age at the time of implantation, radiological evaluations, genetic testing in order to determine whether otoferlin gene mutation was present or not, experience with hearing aid, and ECochG evaluations. In addition, the postoperative indicators consist of obtaining ECAP during the CI surgery or conducting electrophysiological tests such as EABR post-implantation.

Chapter 5

Summary and Conclusions

ANSD includes a heterogeneous population that varies with etiologies and sites of lesion. Due to the limited benefit of CI in children with ANSD, there is a need to identify these children early for a timely transition from hearing aids to other intervention strategies. This would be crucial for the achievement of maximum potential in terms of speech and language development. A review of the literature was conducted using search parameters, and inclusion/exclusion criteria were set. Possible keywords, related search words, and their derivatives relevant to the research question were developed and selected. This review aimed to identify indicators that can help determine eligible candidates with a good prognosis. Thus, a total of 17 articles were considered for the systematic review.

Pre-operative and early post operative CI indicators were identified to predict the outcome of CI in ANSD children. Pre-operative indicators consisted of age at the time of implantation, radiological evaluations, genetic testing to determine whether otoferlin gene mutation was present or not, experience with the hearing aid, and ECochG evaluations. In comparison, postoperative indicators consist of obtaining ECAP during the CI surgery or conducting electrophysiological tests such as EABR post implantation. This review is a guide not only for audiologists but speech-language pathologists and other early interventionists who work with individuals with ANSD and/or their families. It highlights the need to include more precise tools to describe the site of lesion and to identify ANSD candidates with a better prognosis of auditory performance and speech perception.

5.1 Implication of the study

By signifying adequate CI results in ANSD patients with OTOF mutations, this review confirms the usefulness of including genetic diagnostic tests. These findings have important clinical implications: genetic examination should be a part of the pre-CI evaluation battery in ANSD to identify suitable CI candidates. This, in turn, would improve CI outcome prediction capabilities. CT and MRI emerged as reliable pre-operative predictors of speech perception abilities in children with ANSD who underwent CI. ESR and ECAP, early postoperative electrophysiological tests, were also found to predict speech perception abilities for children with ANSD. However, a long-term follow-up is required to arrive at concrete conclusions. Hearing aid trials with ANSD patients should be made a compulsion and only those who derived "intermediate benefit" from hearing aids usage and regular Auditory Verbal Therapy should be considered for a cochlear implant. Better classification of the site-of-lesion in ANSD will allow clinicians to develop more appropriate management options. There has been a surge in identifying tools to define the lesion site in ANSD cases. This fact has also been indicated by a study on Diffusion Magnet Resource Imaging. Such imaging techniques may supplement the existing battery of tests to characterize the site of lesion and extent of dysfunction in individuals with ANSD (Zanin et al., 2020).

5.2 Limitations of the study

The present review had certain limitations. First, the included studies were mostly retrospective in nature. The articles included consisted of case reports and case series. Studies of this nature might be subjected to significant selection and reporting biases. In addition, observational studies are susceptible to extraneous variables which can partially or completely contribute to the observed results.

Studies with comorbidities were excluded thus correlation of these comorbidities on predictors can't be estimated. Due to the retrospective nature of the study, the long-term outcomes of the implantation were not available in all the patients. CAP and SIR scores are not sensitive enough to show subtle changes in the auditory performance and speech production, although they are global measures to evaluate outcomes of CI in children. Additionally, the "early-intervention" strategy might not work with certain uncommon OTOF mutations related to less severe or fluctuating hearing levels; thus a longer period of observation of these patients may be necessary to ensure that indications for cochlear implantation are fulfilled. Although a salient concern, this review only included studies published in English.

5.3 Future Directions

With continued advances in technology, there is a need to discover tools that can provide more definitive answers regarding etiology and predicted outcomes as well as methods to improve audibility and speech clarity for clients with ANSD. However, the absence of conclusive information in this area should not be used to restrict the use of CI in children with ANSD as current evidence points towards benefit in such children. Better evidence is needed to support cost-effective practice in this important area. 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 the future, the development of a clearer stratification system into pre, post, and central ANSD would have clinical and academic benefits.

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