AN UPDATE ON MANAGEMENT OF CHILDREN WITH AUDITORY NEUROPATHY SPECTRUM DISORDER: A SYSTEMATIC REVIEW OF LITERATURE

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This Dissertation is submitted as part of

fulfilment for the Degree of Master of Science in Audiology

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CERTIFICATE

This is to certify that this dissertation entitled **'An Update on Management of Children with Auditory Neuropathy Spectrum Disorder: A Systematic review of literature'** is a bonafide work submitted as a part for the fulfilment for the degree of Master of Science (Audiology) of the student Registration Number: 19AUD029. 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.

Mysuru
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DECLARATION

This is to certify that this dissertation entitled **'An Update on Management of Children with Auditory Neuropathy Spectrum Disorder: A Systematic review of literature'** is the result of my own study under the guidance of Dr K. Rajalakshmi, 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.

Mysuru
September 2021

Registration Number: 19AUD029

DEDICATED TO

Achan, Amma, Anju &

Nandu…

Acknowledgments

"Arriving at one goal is the starting point to another" - John Dewey

First of all, I would like to thank ***God Almighty*** *for all the good and bad times, and lessons learned, all those memorable days during the two years of my MSc life.*

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ABSTRACT

Auditory Neuropathy Spectrum Disorder (ANSD) is a hearing disorder caused due to the dysschynchronous neural firing. The disorder has serious impact of speech perception which gets further worsened in the presence of noise. The current review aimed to document the evidences and outcomes of management of children with Auditory neuropathy. The literature was performed in various databases and up on undergoing further filering and screening seventeen articles that reported the management of ANSD in children were finalized for the review. As reported in the previous review articles, the management options of were cochlear implants and hearing aids. Different objective and subjective tools can be used to monitor and document the benefit of device fitting, which also helps clinician in planning the habilitation and training activities. Measures evaluating neural synchrony at the level of auditory cortex is considered as good predictor of device benefit and real-time correlate of speech identification performance. After undergoing detailed clinical evaluation as well as monitoring the benefits of fitted device/s and incorporation of compensatory strategies, environmental modifications and lip reading and multimodality training as per the requirements and comorbid disorders present in the child would enhance effectiveness of management undertaken.

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Chapter 1

INTRODUCTION

Auditory neuropathy refers to a unique hearing disorder in which neural conduction is impaired with normal cochlear amplification. The condition's clinical diagnosis will be based on the presence of otoacoustic emissions/cochlear microphones and the absence/abnormality of auditory brainstem responses (Starr et al., 1996). At first, the disorder was termed auditory neuropathy, as most affected individuals were reported to have associated peripheral neuropathy. Later, in view of the lesion restricting to inner hair cells in some cases (Miyamoto et al., 1999), the term auditory dys-synchrony was suggested (Berlin et al., 2003). Sininger and Hayes (2008) suggested the term auditory neuropathy spectrum disorder (ANSD), considering that the damage is not confined to a particular site in most of these persons; instead, there are different affected loci. Henceforth in this article, the condition will be uniformly referred to as ANSD.

A varied prevalence ranging from 0.5 to 11 % have been reported by many western studies (Kraus et al., 1984; Berlin et al., 2000; Cone-Wesson & Rance, 2000). In the Indian scenario, among the individuals diagnosed with sensorineural hearing loss, the prevalence of ANSD is reported to be 1 out of 183 patients with SNHL (Kumar and Jayaram, 2006). ANSD can be diagnosed in newborns as well as it can take up an adulthood onset of a late onset of the disorder (Kumar and Jayaram, 2006, Sininger and Oba, 2001, Prabhu et al., 2012, Shivashankar et al., 2003, Berlin et al., 2010).

The site of lesion is not often limited to a single locus in ANSD. It can be due to lesion at the level of inner hair cells of the cochlea, or the synaptic junction of inner hair cells and the auditory nerve, reduction in the neurons in the auditory brainstem, the disorder of spiral ganglion cells, and auditory nerve demyelination (Starr et al., 1996; Rance et al., 2004).

Varied audiological profiles have been reported in the ANSD population. It ranges from normal hearing to even severe to profound degree (Rance et al., 1999). Audiogram of these individuals exhibited a bilaterally symmetrical pattern of hearing loss (Oba & Sininger, 2001). Most of the cases showed to have mild to moderate sensorineural hearing loss (Starr et al., 1996) though the configuration is variable, usually reverse sloping audiogram or a 2kHz peaked audiogram is seen (Narne et al., 2014; Berlin et al., 2010; Kumar & Jayaram, 2006).

Middle ear muscle reflexes or acoustic stapedial reflex are reported to be present in very few individuals with ANSD (Starr et al., 2000, Cheng et al., 2005). A study done by Kumar and Jayaram (2005) revealed an absence of stapedial reflexes in the ANSD population. The afferent pathway's inability to elicit a synchronous neural firing that triggers the stapedial muscle contraction could be attributed to the absence of stapedial reflexes in individuals with ANSD. The efferent pathway of the stapedial reflex arc could be considered intact and normal in ANSD if the non- acoustic stimulations could elicit stapedial reflexes (Star et al., 1998). Higher mean amplitude of TEOAEs compared to normal hearing individuals were reported by Berlin et al. (2003) & Jayaram & Kumar (2005), which is attributed to the lack of intact efferent suppression in ANSD. Deterioration or reduced amplitude of OAEs have been reported in long-standing ANSD (Deltenre et al., 1999). The lack of efferent suppression and absence of acoustic stapedial reflexes, which plays a key role in the protection of cochlear hair cells, might result in a gradual deterioration of OAEs as an effect of damage to OHC over time (Star et al., 1996). Other reported causes of OAE amplitude reduction are the effect of OTOF mutations in OHCs or could be due to hearing aid usage (Rodriguez- Ballestros et al., 2003). The peripheral functions in ANSD could be confirmed by performing Electrocochleography (EcochG) (Arslen et al., 1997). The presence of summating

potential in EcochG points towards the intact functioning of inner hair cells (Durrant et al., 1998).

The speech perception performance observed in individuals with ANSD is disproportionate to the degree of hearing loss (Starr et al., 1996). It is mainly dependent on the extent of successful coding of temporal changes happening in a speech signal over time (Zeng et al., 2005). It was also reported that individuals with peaked audiogram at 2 kHz showed better speech discrimination scores compared to those with other audiometric configurations (Jijo & Yathiraj, 2012; Jayaram and Kumar 2005).

One of the prominent features observed in the ANSD population is their difficulty in speech perception, which worsens in noisy situations or in the presence of competing signals (Zeng et al., 2005, Starr et al., 1996). Deficits in the temporal resolution cause the poor perception of dynamic and short auditory signals (Kraus et al., 2000). Acoustic cues like formant transitions, burst duration, and voice onset time are likely to be affected, leading to poor perception of consonants, mostly plosives/stops (Jayaram and Kumar, 2011).

Rance et al., (2002) reported a correlation of auditory evoked cortical potential with speech perception abilities in ANSD individuals. Those with measurable speech scores showed significantly better morphology and appropriate latency of peaks in late latency responses than those with poorer speech perception scores. Thus, it was concluded that recording a late latency response helps in predicting the speech perception scores. The authors hypothesized that the contributing factor for better speech perception might be the preserved synchrony at the cortical level.

The currently available management options for ANSD are amplification devices and cochlear implantation. A review of literature conducted by Roush et al. (2011) evaluated the outcomes of children with ANSD who underwent conventional amplification

management versus cochlear implantation. Out of the literature obtained, only 13 % of the studies that included case-control and case studies had reported having only amplification devices as an option for management. Other studies reported cochlear implantation alone or cochlear implant along with hearing aid (bimodal fitting) as a management option. Those studies reported cochlear implantation as outcomes revealed comparatively better outcomes in aided pure tone thresholds, speech identification scores, and improved speech and language skills in a longer time period. It has been a decade since the last systematic review on the management in children with ANSD has been conducted. There was heterogeneity of studies that included case studies and case series and full-length original research articles among the literature chosen for the review. Considering the limitations of the previous review and to bring about an update on management strategies and their outcome in children with ANSD, the current paper aims to conduct a systematic review of literature on the updates in the management of children with Auditory Neuropathy Spectrum Disorder.

1.1 Research Questions:

- To obtain information on recent advancements in the management of children with ANSD,
- To obtain updates on audiological outcomes of cochlear implants and hearing aids in children with ANSD from literature published within the last ten years.

Chapter 2

METHODS

A review of the literature was conducted from November 2020 to March 2021 by incorporating the appropriate inclusion and exclusion criteria. An electronic literature search was carried out in the following databases: Google Scholar, Pubmed, Science Direct, Pubmed-Central, J-Gate and a manual google search. All the articles that mentioned management outcomes of children with ANSD were considered from preliminary search and further screening. Articles published from 2011 till the present was considered. The keywords/MeSH (Medical Subject Headings) used for literature search in Pubmed were as follows: (("cochlear implantation"[MeSH Terms] OR ("cochlear"[All Fields] AND "implantation"[All Fields]) OR "cochlear implantation"[All Fields]) AND ("auditory neuropathy"[Supplementary Concept] OR "auditory neuropathy"[All Fields] OR "auditory neuropathy"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields])) NOT ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields] OR "adult s"[All Fields]), ((("hearing aids"[MeSH Terms] OR ("hearing"[All Fields] AND "aids"[All Fields]) OR "hearing aids"[All Fields] OR ("amplificate"[All Fields] OR "amplificates"[All Fields] OR "amplification"[All Fields] OR "amplifications"[All Fields])) AND ("auditory neuropathy"[Supplementary Concept] OR "auditory neuropathy"[All Fields] OR "auditory neuropathy"[All Fields])) OR "ANSD"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]). For J-Gate, the search terms used were auditory neuropathy: [All] AND cochlearimplantation: [All],auditoryneuropathy: [All] AND a

mplification: [All],auditoryneuropathy: [All] AND Brainstem-implant: [All], auditory neuropathy: [All] AND hearing aids: [All]. For Pubmed Central, the search builder used for literature search was ((((((auditory neuropathy) AND cochlear implantation) OR amplification) OR hearing aids) OR brainstem implants) AND children) NOT adults. The search terms allintitle: auditory neuropathy spectrum disorder "cochlear implantation", allintitle: auditory neuropathy spectrum disorder "amplification", allintitle: auditory neuropathy spectrum disorder "hearing aids", and allintitle: auditory neuropathy spectrum disorder "brainstem implants" were used to search literature in Google Scholar. Moreover, the search terms for Science Direct were auditory neuropathy AND cochlear implantation, auditory neuropathy AND amplification, auditory neuropathy AND Brainstem implant, auditory neuropathy AND hearing aids.

Eligibility criteria for inclusion of articles were as follows: (1) articles published in English, (2) availability of full-text material, (3) studies involving human subjects, (4) studies including children less than 14 years of age.

(5) Selection criteria were based on PICOS (Methley et al., 2014).

P- Population – Children with Auditory Neuropathy Spectrum Disorder and diagnosis have been done using the appropriate test battery approach.

I – Intervention – Intervened using hearing aids/cochlear implants/brainstem implants.

C- Comparison- Other groups like children with SNHL, provided the articles have reported separate data analysis for each group.

O- Outcome- Treatment outcomes evaluated using appropriate objective and subjective tests.

S- Study design – Retrospective, case-control, cohort studies were included.

T- Timings: The articles published over the last 10 years (from 2011 to 2021) were included.

Exclusion criteria were as follows:

(1) articles reporting case studies and case series were excluded.

(2) Studies including adult and geriatric population and animal studies.

(3) Letters to editors, short communications, and systematic reviews.

(4) Studies that have reported etiologies other than ANSD causing hearing loss (like conductive, mixed, cochlear/ retro cochlear pathologies) have conducted a combined analysis of intervention outcomes.

2.1 DATA EXTRACTION:

Two independent reviewers (Praveen Prakash and Athul P.R) performed the data extraction to avoid bias. The duplicates were removed using reference manager software Mendeley. The articles obtained after searching various databases were undergone a title screening and abstract screening. Later, considering the mentioned inclusion and exclusion criteria, the remaining articles underwent full-text screening. The number of articles were finalized after performing qualitative analysis. The PRISMA guidelines were followed for screening the articles (Moher et al., 2009).

2.2 QUALITY ANALYSIS (Risk of bias):

The quality assessment was performed by two reviewers to avoid the risk of bias. The NIH quality assessment tool was used to perform the quality analysis. The NIH tool kit had individual tools for Observational cohort and cross-sectional studies, case-control studies, and Before-after studies(pre-post) comparison without a control group. The former tool had fourteen questions, and the latter two had twelve questions, respectively. The questions were provided with yes/no/other options to be answered

after considering each article. Among the three tools mentioned above, each tool was chosen to evaluate article based on the type of study mentioned in the article. Each reviewer had to rate every article with a final rating as ‘Good’, ‘Fair’, or ‘Poor’ and it was planned to approach a third reviewer if there were discrepancies between the results of the reviewers. However, there were not much significant differences between the ratings of initial two reviewers and thus a third review for risk of bias was not required. These were some of the examples of the questions: “*Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?, Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?”, “Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?”*

Chapter 3

RESULTS

A total of 2405 studies were obtained after conducting the searches in all the above-mentioned databases out of which 755 were duplicates. About 1650 articles underwent title and abstract screening and finally 38 articles were selected for full text reading. Appropriate inclusion criteria and exclusion were considered in the full text screening and 17 articles were opted for the review. The quality analysis was carried out by two reviewers and 10 articles were rated as ‘good’ and remaining were rated ‘fair’ and two articles which had ‘poor’ quality were excluded as the sample size taken were small (N= less than 5). No other articles were rejected based on quality analysis. Figure 3.1 demonstrates the article selection procedures starting from literature search results to finalizing the articles for review. Table 3.1 shows the articles selected for final review and their Quality analysis. Table 3.2 demonstrates the summary of studies that had performed as well as evaluated the management and its outcome in children with ANSD.

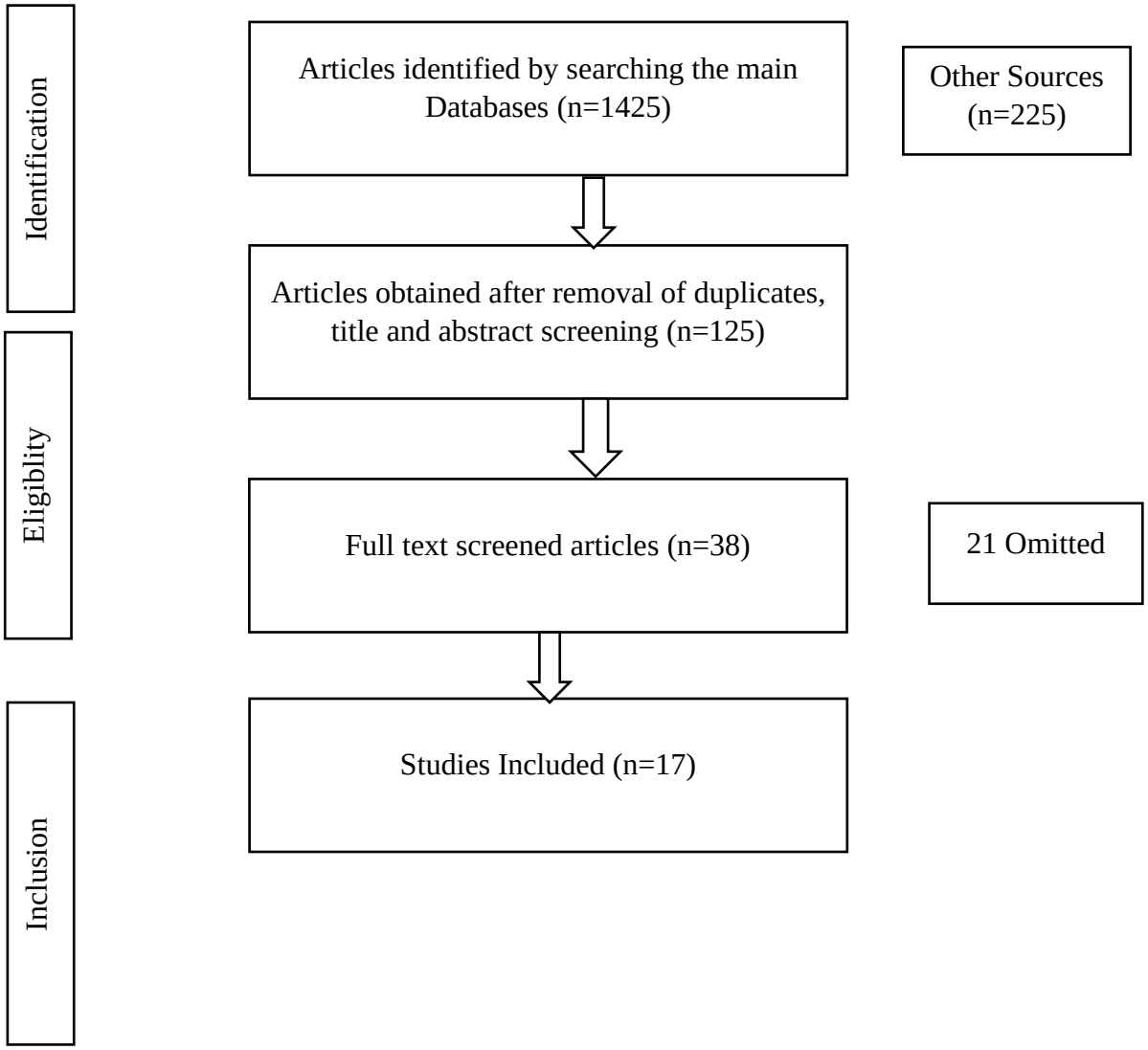

Figure 3.1: PRISMA chart showing processes carried out in finalization of articles.

Sl. No	Author	Year	Country	Management done	No. of subjects	Type of study	Quality Analysis
1.	Alvarenga et. al	2012	Brazil	Cochlear Implantation	14	Cross-sectional	Good
2.	Cardon and Sharma	2013	U.S.A	Cochlear Implantation	35	Cross-sectional (N=24) + Longitudinal (N=11)	Good
3.	Sinha et al	2015	India	Cochlear Implantation	42	Longitudinal	Good
4.	Kim et al	2011	Korea	Cochlear Implantation	10	Cross-sectional	Fair
5,	Shaikh et al	2016	Egypt	Cochlear Implantation	17	Cohort study	Fair
6.	Daneshi et al	2018	Iran	Cochlear Implantation	136	Longitudinal	Good
7.	Breneman et al	2012	U.S.A	Cochlear Implantation	70	Retrospective study	Fair
8.	Carvalho et al	2016	Brazil	Cochlear Implantation	10	Cohort study	Fair
9.	Attias et al	2016	Israel	Cochlear Implantation	32	Cohort study	Good
10.	Nash-Kille et al	2013	U.S.A	Cochlear Implantation	182	Case-Control	Fair
11.	Hassan	2016	Egypt	Hearing Aid	45	Cross-sectional	Fair
12.	Sharma et al	2011	U.S.A	Hearing Aid	21	Cross-sectional	Fair

13.	Walker et al	2016	U.S.A	Hearing Aid	24	Prospective+Longitudinal	Good
14.	Budenz et al	2013	U.S.A	Cochlear Implantation	17	Retrospective	Good
15.	Kontorinis et al	2014	U.K	CI + HA	27	Retrospective	Fair
16.	Alzhrani et al	2019	Saudi Arabia	Cochlear Implantation	58	Cohort study	Fair
17.	Greisiger et al	2013	U.SA	Cochlear Implantation	16	Case-Control	Fair

***Table 3.1*:** Demographics of articles and results of quality analysis performed by the reviewers.

Sl. No	Author	Age range of subjects	Interventions	Assessment Tools	Findings and Implications
1.	Alvanegar et al	4-11 years	CI	LLAEP synthesized speech stimuli /ba/. P1 component of the waveform was identified and analysed. GASP was used to evaluate the speech perception abilities of the subjects.	The P1 component was present in 85.7% of the subjects. Presence of p1 implicates the speech perception abilities, the electrical stimulation by cochlear implant supplies impulses to the dys-synchrony present due to Auditory neuropathy. A longer p1 latency duration was positively correlated with duration of auditory deprivation. The absence of P1 component was correlated with scores obtained by the subjects for GASP.
2.	Cardon and Sharma	1.4-12.6 years	CI	IT-MAIS and CAEP were assessed. CAEP used synthesized speech stimulus	P1 was present with significant amplitude, latency, and replicability in all children. Children who underwent implantation during early ages of life had normal p1 latency and late implantees had delayed p 1 peaks.

				/ba/. P1 component of the waveform was analysed.	ITMAIS improved scores were exhibited by early implantees and comparatively lower scores obtained by late implantees. IT MAIS performances and p1 latency and presence of cortical response indicates auditory maturation at cortical level and hence the auditory development of children with ansd post cochlear implantation. Longitudinal results of 11 subjects: the authors compared the P1 of CAEP pre and post implantation. 10 out of 11 children showed improvement or normal findings of P1 latencies.
3	Sinha et al	<12 years	CI	Categories of Auditory Performance (CAP) assessment was carried out before	Post 6 months given for assessing hearing aid benefit, 15 out of 42 children reported good benefit, 13 reported intermediate benefit and 14 reported no benefit.

				implantation while the children were recommended to undergo hearing aid fitting and auditory training for 6 months. Those with intermediate and no benefit underwent cochlear implantation. Those with good benefit from hearing aid was recommended to continue using hearing aid. 6 months later, CAP were re-administered to evaluate the device benefit and progress of children.	6 months post cochlear implantation, all 13 children were administered with CAP and showed good benefits. The authors made the children undergo a trial period with hearing for realistic benefit trial and those who benefited were asked to continue the use of hearing aids and others were recommended with CI which highlights those children who are not benefitting from ha are likely to benefit from CI.

4.	Kim et al	<9 years	CI	ECAP recovery functions of the implanted children who has AN were compared with that of SNHL group. Speech perception scores of AN were measured using monosyllabic word lists.	There was no significant difference in ECAP recovery function in ansd children when compared to SNHL population. Refractoriness of auditory nerve of ansd population is similar to that of SNHL. The faster the recovery rate from the refractory state, the better will be the temporal processing. Cochlear implantation resulted better temporal coding of neural signals in children with ANSD. The authors concluded that ECAP recovery functions can be considered as an outcome measure for cochlear implanted children with ANSD.
5.	Shaikh et al	N/A	CI	AN-N=7, SNHL- N=10 All children undergone therapy 6 months pre-operative period	There was significant auditory development noted in both AN and SNHL groups post implant.

				by using hearing aid and 6 months post implantation respectively. Auditory and speech and language test was done using auditory skills checklist (ASC) and the Arabic language test.	Improvement in receptive and expressive language was also noted. The authors highlighted the effectiveness of electrical stimulation over acoustic stimulation in ansd population and undergoing proper therapy on a regular schedule had markedly improved and auditory as well as language development of the children.
6.	Daneshi et al	≤14 years	CI	48 children were included into group I (undergone implantation before or at the age of 24 months) And 88 were added into group II (children underwent implantation after 24 months)	The follow up evaluations were done at 1st and 2nd year post-operative years which showed significant improvement along with which children in group II had better outcome with same time span post implant. The improvement in the CAP scores during the first year in Group II was greater than Group I. But the improvement in CAP scores tended to be significantly

				CAP and SIR scales were used to assess auditory and speech production skills.	higher in patients who were implanted at ≤ 24 months. The authors highlighted the significant importance of early diagnosis and implantation which led to better prognosis.
7.	Breneman et al	≤14 years	CI	The speech perception test battery included ITMAIS, MAIS Little ears, ESP, and GASP for words and sentences. Depending on the vocabular of the child the tests were carried out NUCHIPS, WIPI, MNLNT, LNT.	Post-operative difference in mean PTA across the groups was 16.71 compared to the pre-operative mean PTA 83.8 for ansd and 97.7 dB for SNHL. Cochlear implant sound field PTA was 19 to 26 dB. Mean speech perception scores for ansd was 81.3 % and for SNHL group was 78.0%. The authors concluded that over a long term period, children with ANSD could achieve benefits from cochlear implantation almost similar or even better than children with SNHL.

8.	Carvalho et al	2-6.1 years	CI	SADL questionnaire was administered to evaluate satisfaction from device usage. it had 15 questions, in which each question were grouped under subsections like, positive effects, service and value, negative factors and personal image.	The cochlear implantation proved to be an effective rehabilitative option as the results of the current study revealed high positive effects and very low effect of negatives on cost and personal life of patients, hence highlighting the satisfaction of patients from cochlear implantation. The authors concluded the efficiency of modern devices are effective in dealing with disability due to hearing impairment and promises satisfaction from the users.
9.	Attias et al	5-12.2 years	CI	Speech perception scores were evaluated in silent as well as in presence in noise using	The results revealed that both the AN and SNHL groups had similar aided hearing scores and performance for speech understanding in quite as well as in noise.

				monosyllables, spondees and everyday sentences. The dynamic range of two groups were compared by calculating the T and C levels.	The ANSD group had lower T levels and C levels compared to SNHL group and a comparatively reduced dynamic range was noted for ANSD group. There was a positive correlation between residual low frequency hearing and current levels at the higher frequencies. As the residual hearing becomes better lower T levels were achieved. The authors highlighted the extend of benefit of cochlear implantation in ANSD population in equivalent to that could be achieved for any profoundly hearing impaired SNHL.
10.	Nash-Kille et al	≤14 years	CI	They measured the neural synchrony to measure the cortical synchronisation to speech stimulus using inter trial	Reduced phase synchrony was noticed in children with ANSD and inter-trial coherence was sufficient to differentiate the responses from normally hearing and ANSD. The authors also point out the lack of coherence

				coherence. And compared the results with that obtained from normally hearing children and those with SNHL.	at cortical level seen in those with severe hearing loss and further states as a correlate for the lack of audibility in severe to profound hearing loss individuals compared to those with mild degrees of hearing impairments. The children with ANSD exhibited low phase coherence compared to those with sensorineural hearing loss and it was also noticed that cochlear implantation and its long-term usage increased the cortical coherence. The study suggests inter-trial coherence as a good tool to evaluate neural synchrony at the level of auditory cortex.
11.	Hassan	48.2 +/- 29.4 months	HA	Subjects were divided into 3 groups : children with ANSD, SNHL, and Normal hearing. The children with ANSD and	The aided PTA was 30+/- 10 dB HL and 27+/- 7 dB HL for ANSD and SNHL respectively. Among ANSD group, 80% and 87% of the children showed significant P1 response to ‘ba’ and ‘da’ stimuli respectively.

				SNHL were fitted with same model of hearing aid and verification was performed using aided sound filed, P1-CAEP using ‘ba’ and ‘da’ stimuli and administering IT-MAIS. The IT-MAIS and P1-CAEP evaluations were conducted 6 months post initial evaluation.	In all the three groups, P1-N2 complex was the dominant waveform morphology in the responses. When comparing the latency across groups 50% of ANSD children had a delay in latency of P1-CAEP. Post 6 months 2 children with ANSD showed improvement in latency. For IT-MAIS, the scores were 45.5+/- 20 for ANSD group and post 6 months a statistically significant improvement was noted in both ANSD and SNHL. However, ANSD showed comparatively smaller improvement with respect to SNHL.
12.	Sharma et al	0.9-11.5 years	HA	They evaluated P1 component of CAEP for speech stimulus /ba/. IT-MAIS was used to	The author concludes the presence of aided P1-CAEP as an indicator for possible hearing aid benefit as it denotes the synchrony at cortical level of the auditory system.

				measure behavioral auditory development.	Neuroplasticity is stimulated with amplification which changes the structural and functional mechanisms of auditory nervous system which is reflected as auditory development and hence an improvement in IT-MAIS scale.
13.	Walker et al	≤11 years	HA	Speech perception and language outcomes were measured using GFTA-2, PPVT-4, The Vineland Adaptive Behavior Scales – II, and CASL. Little EARS was used to monitor auditory development, PBK-list for speech identification testing,	Results of language assessment revealed a significant improvement in receptive as well as expressive language ages of all the three children and extend of progress was equal in all of them and it depended mainly on duration of treatment and chronological age of initiation of intervention program. The authors conclude amplification devices and therapy post fitting aided in development of language in children with ANSD.

				and children with 8- 9 years were tested using CASPA.	
14.	Budenz et al	≤85 months	CI	Children were classified into two groups: with ANSD and Cochlear hearing loss, speech and language outcomes were tested using PLS, EVT, and PPVT	Measures of morphosyntax, pragmatic behavior, and adaptive behavior has almost similar to that of children with SNHL. The speech identification testing resulted in nearly similar scores with SNHlL. But speech in noise testing showed significantly poor scores for ANSD group. The authors imply that ANSD children could benefit from hearing aids if the loss was within moderately severe degree and their aided speech perception showed good results. It could possibly results in auditory, speech and language development in a child with ANSD to the same extent that can be expected for an age matched

					child with similar degree of hearing loss. However, speech perception in noise will still be a challenge for ANSD and incorporation of assistive device with hearing aid will be a good recommendation.
15.	Kontorinis et al	≤11 years	CI, CI+HA	Children's auditory development and spoken language abilities were evaluated using CAP, and MSLDS respectively. The scores of the above were compared with pre-operative and follow up visit post-operative period.	There was a significant improvement noted in speech and language outcomes in both groups. However, AN group showed comparatively less but within the standard range of expected level of performances for the implant group. The conclusion was made those children who were poor candidate for amplification could possibly benefit from cochlear implantation.

16.	Alzhrani et al	N/A	CI	Subjects consisted on two groups: ANSD and SNHL. Auditory performances were evaluated using CAP and SIR was used for evaluating speech intelligibility.	There were significant improvement in the auditory as well language skills of children post cochlear implantation. the authors further highlighted, apart from unilateral CI, if the unaided ear is meeting up candidacy criteria for having a hearing aid, then the child can be recommended to undergo bimodal fitting which would in turn activates the binaural hearing in users. There was no statistically significant difference for CAP as well as SIR for both groups. All the children were fitted with hearing aid for 4 to 37 months and depending on followed outcomes they were referred for cochlear implantation. Early identification, and redirecting to the most benefitting management would help children achieve auditory as well as speech and language developmental milestones than a lately intervened child.

17.	Greisiger et al	≤12 years	CI	ImpEABR was performed at 220 CL at a pulse rate 25u/s through all 22 electrodes. And the eV of EABR was analysed and compared between the groups.	The amplitudes and latency of eV of EABR waveforms were almost similar among all subjects in both the groups. One child with ANSD had a higher amplitude. This measures the synchrony of the auditory neural coding of stimuli in ANSD, which is required for speech recognition in quite as well as in noise. The authors concluded that achieving an EABR waveform with good morphology and latency is a good predictor of futuristic benefit from the device.

Table 3.2:Summary of selected articles mentioning management, outcomes and overall implications of their findings. (Expansion of abbreviations have been mentioned in the text portion of results section).

3.1 Recent advancement in management of children with ANSD;

Out of the seventeen studies selected for review, thirteen studies have reported outcomes of children who have undergone cochlear implantation only (includes bilateral as well as unilateral), three articles have reported findings in children using hearing aids alone, and only one study has included children using both hearing aids and cochlear implants.

3.2 Outcome measures in children who underwent cochlear implantation and hearing aids:

Outcomes measures in children have been conducted mainly by using three measures: (1) aided sound field thresholds, (2) speech recognition scores and different scales to measure auditory development, (5) speech production and language skills, and (4) Long latency auditory evoked potentials to evaluate cortical maturation which is often correlated with the device benefit and outcomes of speech perception. Only a study by Greisiger et al (2013) has used intraoperative electrical ABR as a measure of synchrony of auditory neural pathway.

In a study by Breneman et al (2012), the post-operative difference in mean PTA across the ANSD and SNHL groups was 16.71 compared to the pre-operative mean PTA 83.8 for ANSD and 97.7 dB for SNHL respectively. Similarly, the aided PTA was 30+/- 10 dB HL and 27+/- 7 dB HL for ANSD and SNHL respectively in a study conducted by Hassan (2016) in children fitted with hearing aids. For evaluating speech perception abilities, The Glendonald Auditory Screening Procedure (GASP), Word Intelligibility by Picture Identification (WIPI), Northwestern University-Children's Perception of Speech (NU-CHIPS), Early Speech Perception test (ESP), Lexical Neighbourhood Test (LNT), Multisyllabic Lexical Neighbourhood Test (MNLNT), PBK-list for speech identification testing, and Computer-Assisted Speech Perception Assessment (CASPA) were used by

various authors. Similarly, for measuring auditory developmental skills post-implant, Categories of Auditory Performance, Infant Toddler Meaningful Auditory Integration Scale, Meaningful Auditory Integration Scale, Auditory Skills checklist, Early Speech Perception, and Little EARS auditory questionnaire were used. Arabic Language Test was used by Shaikh et al (2016), Speech Intelligibility Rate scale was used by Daneshi et al (2018) and Alzhrani et al (2019), and Goldman-Fristoe Test of Articulation-2 (GFTA-2), The Peabody Picture Vocabulary Test-4 (PPVT-4), The Vineland Adaptive Behaviour Scales – II, and comprehensive assessment of spoken Language (CASL), Preschool Language Scale (PLS) and Expressive Vocabulary test (EVT) were used by Walker et al (2016) and Budenz et al (2013) respectively for assessing speech and language outcome measures of children belonging to different age groups. Carvalho et al (2016) conducted a survey on satisfaction of children who have underwent cochlear implantation using Satisfaction with Amplification in Daily Life (SADL) questionnaire. Electrically evoked Compound Action Potential (ECAP) recovery functions were considered a test measure of synchrony and was compared by Kim et al (2011) among children with ANSD and SNHL who underwent cochlear implantation and to compare the outcomes in ANSD children and to correlate with speech perception scores using monosyllabic speech identification. Finally, Long Latency Auditory Evoked Potentials were measured as long-term outcome of device fitting by Alvanegar et al (2012), Cardon and Sharma (2013), Hassan (2016), and Sharma et al (2011) to verify the benefit as well an objective proof stating the auditory maturation that was happening at the auditory cortex resulting appropriate and regular acoustic stimulation which had driven the neuroplasticity.

Among the studies reviewed, all studies reported to have a benefit of undergoing hearing aids or cochlear implant, provided candidacy criteria for the same has been followed efficiently. Significant improvement was noted in auditory, speech and language

development post fitting of devices/implantation. Daneshi et al (2018) compared the cortical responses to speech sound of children who underwent early implantation (<2 years) and late implantation (>2 years) and identified that early implantation tiggers neuroplasticity more efficiently and enhanced development of auditory cortex compared to late implantees which were evident from the P1 component of LLAEP waveforms. Nash-Kille et al (2013) pointed out inter trial coherence in LLAEP as a marker of cortical synchrony and associated neural maturation of cochlear implanted children with ANSD. The cortical synchrony is said to be the factor that is contributing to coding comprehension of speech and a lack of this coherence is associated with poor speech perception outcomes and device benefit. Most of the authors had performed hearing aid trial or aided cortical response to speech stimulus as a measure for hearing aid verification prior to proceeding for cochlear implants in children who had sensorineural hearing loss less than or equal to severe degree. Sinha et al (2015) conducted a trial on children for 6-month period to assess the benefit of hearing aid and later in subject who showed poor benefit or intermediate were asked to undergo cochlear implantation. Those children who showed good benefit from using hearing aids were recommended to continue the use of hearing aid and extensive auditory training. Whereas, a study reported by Hassan (2016) revealed children fitted with hearing aid alone had good auditory developmental outcomes.

While almost all authors reported improved speech understanding post device fitting, a study by Budenz et al (2013) revealed comparatively poorer performance of children with ANSD in speech perception tests administered in the presence of competing noise in comparison with children with SNHL. Speech understanding in noise in a phenomenon which demands higher level of neural synchrony and considered a challenging in children with ANSD. Greisiger et al (2013) reported wave V obtained in eABR is a good indicator

for higher level or neural synchrony at the level of brainstem and hence point at enhanced performance for speech in noise tasks.

Chapter 4

DISCUSSION

Management of auditory neuropathy has always been a challenging process for the audiology practitioners. The multi-site lesion and varied severity and overall heterogeneity in hearing thresholds and speech identification scores among the patients leads to difficulty in choosing the most appropriate option in the initial stage of rehabilitations (Starr et al., 1996; Rance et al., 2004).

It is recommended to conduct a detailed audiological evaluation to rule out the possible site of lesion and extend of residual functional integrity of cochlear hair cells and auditory nerve, the terminal portions of the ascending peripheral auditory pathway which are considered to be the major contributors to the disorder. Pure tone audiogram, immittance evaluation which includes assessment of middle ear functioning and functional intactness of acoustic reflex pathway, along with carrying out Otoacoustic emissions will reveal the severity, type, pattern of hearing loss, and hints regarding possibility of any pathology up to the level of lower brainstem. Auditory brainstem response, which is a test of synchrony is the gold standard test for identification of auditory neuropathy as the disorder has highest impact on synchronous firing on auditory nerve fibres. An absent or abnormal ABR waveform with the preserved functioning of cochlear outer hair cells is suggestive of auditory neuropathy (Starr et al., 1996; Rance et al., 2004; Starr et al., 1999). Hence presence of robust OAE and absence of ABR in new-born infants even 3 months of age is highly likely scenario for a diagnosis of AN.

Factors such as toxic metabolic (hyperbilirubinemia and hypoxia), infectious, genetic, and immunological factors like drug reactions and demyelination have been listed as possible aetiologies of auditory neuropathy (Starr, Sininger, & Praat, 2000; Berlin et al., 2010; Starr, Zeng, Michalewski, & Moser, 2008;). The onset of most cases of AN were

considered idiopathic in nature (Starr et al., 1996). But recent technological advancements in the field of human genetics and enhancement of detailed genetic evaluations have revealed a significant contribution of genetic factors and pathogenic mutations causing auditory neuropathy (Manchaiah et al, 2011). Many literatures have revealed that pathogenic mutations of GJB2, OTOF, and DIAPH3 genes have been traced in individuals with ANSD (Tang et al., 2017). Apart from these genes, novel mutations of SLC26A4, PJVK, A1FM1, Connexin26, OPA1 and SX010 have been documented as predisposing genetic factors of auditory neuropathy (Bae et al, 2013; Rajput et al,2019). Other conditions like low birth weight, low APGAR score, ototoxic drug regimen, hyponatremia, and anoxia (Leonardis et al. 2000; Berlin, Hood, Morlt, Rose, & Brashears, 2002).

Like any other congenital hearing impairment, an early diagnosis and rehabilitation is mandatory for children with ANSD. Amplification devices, cochlear implants, and assistive listening devices for signal-to-noise ratio enhancement have been proved to be effective management options for AN (Roush et al, 2011). Undergoing a hearing trial to cross-check the possibility of benefit from amplification devices is performed prior to cochlear implantation (Abusetta et al, 2016). Aided speech perception scores and speech sound evoked cortical potentials have showed to be a reliable behavioural measure of synchrony at the level of auditory cortex (Cardon and Sharma, 2013). If found not benefitting from hearing aid usage, those children are recommended to undergo cochlear implantation. Post management there is a need to monitor the outcomes to ensure successful rehabilitation and also to evaluate the quality of existing practice and look for further requirement of any modifications is therapeutic approaches for the children.

In the current review, various authors have reported the use of a number of subjective as well as objective tools for monitoring the efficacy of treatment of children with ANSD.

Categories of Auditory Performance, LittleEARS auditory questionnaire, Speech Intelligibility rating, Infant-Toddler Meaningful Auditory Integration Scale, Meaningful Auditory Integration Scale, Early Speech Perception test are the main subjective tools that were used for evaluating the auditory, speech and language development post rehabilitation in children. Objective tools that were reported were tracing latency and morphology of the P1 component of CAEP was shown to be most reliable evidence for auditory development and neural synchrony of auditory cortex which is a consequence of neuroplasticity triggered by acoustic/electrical stimulation via the fitted devices. It had good correlation with the other subjective tests used for evaluating auditory and speech and language development (Cardon and Sharma, 2013; Alvarenga et al, 2012; Hassan, 2017). Nash-Kille et al reported inter trial coherence as a marker of synchrony at cortical level. Moreover, the morphology of waveform tends to directly correlate with the speech perception scores and hence the morphology of the P1-N2 complex of CAEP acted as a predictor of better versus poorer speech identification scores.

There are numerous factors that influence the auditory speech and language developmental outcomes of treatment for ANSD. Conditions like Fredrich Ataxia, Charcot-Marie-Tooth disease, Gullian Barre syndrome, and Rufson syndrome has reported the incidence of associated auditory neuropathy in several patients (Starr et al., 1996). These conditions could have possible comorbid sensory, behavioural, or cognitive involvement which in turn affects the treatment results provided to these patients. In the current review, articles containing subjects with other comorbidities were excluded for the homogeneity of the results and deriving reliable implications from the studies. Other behavioural disorders like Attention Deficit Hyperactive Disorders, Autism spectrum disorder, Cerebral Palsy, and Intellectual Deficit have potential impacts focus, attention, comprehension, memory etc., which are pre-requisites for learning (Colomer et al, 2017).

A properly structured and regular Auditory Verbal therapy should be provided for children post device fitting (Edwards, 2016). Achievement of auditory milestones should be tracked using validated tools like IT-MAIS, CAP, MAIS, and LittleEARS depending on the listening age of the child.

In the current review, majority of the articles reported cochlear implantation as a management option whereas two articles had hearing aid users as the subjects. Also a study done by Alzhrani et al (2019) reported subjects undergone cochlear implantation as well as hearing aid if the non-implanted ear was aidable (bimodal fitting) (Alzhrani et al, 2019). A study by Daneshi et al, (2018) stated the importance of undergoing early implantation and its significance in outcomes. The possible explanation for this the earliest age at which the auditory stimulation is initiated, the neuroplasticity and critical period for neural maturation is in its highly active phase during ages less then 4-5 years. Hence, an early implantation could results in comparatively faster rate of progress in treatment. Another two studies by Kim et al, (2011) and Greisiger et al (2013) reported ECAP recovery functions and presence of eV peak in intraoperative eABR waveform respectively to evaluate the level of synchrony at the level of auditory nerve. Another area of required outcome measurement is evaluation of social, emotional, academic and possible psychological outcomes of children having Auditory neuropathy. A study by Carvalho et al (2016), used SADL questionnaire to rate the quality of children with ANSD who had undergone cochlear implantation. The results revealed that the positive effects were very high, with very low negative factors, costs or negative effects on personal image of the patients, indicating that cochlear implantation proved to be good for children with auditory neuropathy. Opting appropriate treatment option and intensive auditory training can result in better outcomes for ANSD children which is almost similar to the children with SNHL fitted with cochlear implants and/or hearing aids.

Chapter 5

SUMMARY AND CONCLUSION

The current review focussed on articles published since last ten years on management of Auditory neuropathy spectrum disorder in children. Seventeen articles were finalized after going through an extensive search and filtering of literature. Cochlear implants and hearing aids have been extensively reported to be effective in management of ANSD. But as the clinical characteristics and sites of lesion of the disorder are heterogenous, the outcomes varies for each individual as well as the therapeutic strategies have to be tailored individual specific. ANSD is a disorder in which the neural synchrony in the auditory pathway is compromised. The degree of dys synchrony is also a predictor of the outcomes and assistance of further additional modalities like visual cues required for comprehension of speech even after undergoing with fitting of devices like hearing aids and/or CI. The synchrony of neural firing at the cortical level is a direct correlate of speech identification performance and many literature who studied the cochlear implantees on a longitudinal basis had demonstrated improved synchrony with long term duration usage which was eviedent from the latency, morphology and amplitude N1-P2 complex evoked in response to speech stimulus. However, providing listening training to these children would require the assistance of visual modality or even multimodality in cases if comorbid developmental disorders are present in a child with ANSD. Usage of hearing aids alone and in combination with cochlear implant (bimodal fitting) have also been reported to be beneficial. Aided cortical responses to speech stimuli and the extend of robustness could be taken as a predictor for better outcomes from hearing aid use.

Other parameters like inter trial coherence of long latency responses, electrically evoked Auditory brainstem responses, improvement in eCAP waveforms are few of the other indicators of successful device fitting. And more than anything subjective evaluations of

behavioral outcomes, tracing the improvements in auditory development post device fittings, modifying strategies based on aided speeh identification performances are other methods to be taken care of by the clinicians while dealing with the management of children with auditory neuropathy.

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