ONE YEAR PREVALENCE OF AUDITORY NEUROPATHY SPECTRUM DISORDER IN CHILDREN

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17AUD016

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Dedicated to
My Guide and
My Family

CERTIFICATE

This is to certify that this dissertation entitled "**One year prevalence of auditory neuropathy spectrum disorder in children**" is a bonafide work submitted as a part for the fulfilment for the degree of Master of Science (Audiology) of the student Registration Number 17AUD016. 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.

Mysore

May, 2019

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CERTIFICATE

This is to certify that this dissertation entitled "**One year prevalence of auditory neuropathy spectrum disorder in children"** 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 **"One year prevalence of auditory neuropathy spectrum disorder in children"** is the result of my own study under the guidance of Dr. Prawin Kumar, Associate 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: 17AUD016**

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Abstract

Auditory neuropathy spectrum disorder (ANSD) is an auditory deficit which is attributed by altered or absent auditory brainstem response and middle ear muscle reflexes which suggests an asynchronous firing of the auditory nerve; presence of otoacoustic emissions and/or cochlear microphonic which reflects the near normal cochlear amplification. The current study was aimed to estimate the prevalence of ANSD in children up to the age of 12 years, reported at All India Institute of Speech and Hearing, Mysuru between 1st January and 31st December 2018. A retrospective study was conducted by reviewing case files of 1147 children with and without hearing loss and the demographic details and other evaluation findings were noted down. Results showed that out of 995 hearing impaired children, 747 (65.13 %) children had either unilateral or bilateral sensorineural hearing loss (SNHL) of variable degree. Out of the diagnosed SNHL cases, 8 of them were diagnosed to have ANSD i.e. 1 in 124 (0.8 %) hearing impaired children and 1 in 93 (1.07%) children with sensorineural hearing loss. Remarkably all the children with ANSD had at least one risk factor which yields to pathological changes and hyperbilirubinemia was found to be the most prevalent one. Hence, from the current study findings it can be concluded that ANSD prevalence is 1.07% in children and it is not an infrequent auditory disorder in paediatric population. Therefore, it is necessary to have a comprehensive evaluation as well as rehabilitation strategies for children with ANSD.

Chapter 1

Introduction

Auditory neuropathy spectrum disorder (ANSD) is relatively a novel terminology proposed for those patients who have auditory disorder due to impaired auditory nerve or synapse of auditory nerve and inner hair cells of cochlea (Hayes, Sininger & Northern, 2008). It is one of the auditory deficits which are characterized by an abnormal or absent auditory brainstem response (ABR) and presence of otoacoustic emissions (OAEs) / Cochlear microphonic (CM). Altered ABR is seen especially at higher stimulation rate which suggests an asynchronous auditory nerve fibres firing. However, the presence of OAE/ CM is a reflectance of preserved cochlear amplification. Along with these discoveries, Berlin and his colleagues in year 2003 recommended normal tympanometry and absent acoustic reflexes of middle ear muscle (which is an indicative of an asynchronous auditory nerve firing) can also powerfully suggest 'auditory dys-synchrony,' which was the term proposed as an alternate to auditory neuropathy.

Starr and his colleagues in the year 1996 proposed the term 'Auditory neuropathy' to define their 10 patients who had acquired hearing loss with normally functioning cochlea. All these patients had peripheral neuropathy which was developed later in life. In order to confirm their diagnosis they considered the pre-neural responses (cochlear microphonic or otoacoustic emissions) which are present with an absent auditory brainstem evoked responses. From their findings they came to the conclusive terminology of ANSD with normal outer hair cells functioning, with impaired auditory nerve firing. The usage of the term ANSD was recommended by a panel of professionals in Como, Italy during the New-born Hearing screening

Conference in the year 2008. The term is used to represent the disturbances in anatomical and functional aspects in the impaired individuals. Advanced techniques for measuring the outer hair cells functioning have made it less difficult to detect the disorder which is featured by impaired temporal encoding (Zeng, Oba, Garde, Sininger & Starr, 1999) and asynchronous neural firing.

It could be concluded that, neither "auditory dys-synchrony" nor "auditory neuropathy" is suitable to define those individuals with altered auditory brainstem responses and near normal cochlear responses (Rance, 2005). There are significant controversies exist regarding all aspects of ANSD including its cause, site of lesion, management and even the terms which are used for explaining the condition (Rousch, Frymark, Venediktov & Wang, 2011).

1.1. Aetiology and pathophysiology of Auditory Neuropathy Spectrum Disorder

In most cases, ANSD is associated in combination with particular medical risk factors, still the exact site of a lesion and the pathophysiological changes of ANSD are not totally identified. Research findings suggested that this can be due to impairment in structures such as inner hair cells, VIIIth nerve or spiral ganglia (Berlin et al., 2010). Some children who exhibit ANSD may have congenital disorders which are the result of prenatal or perinatal causes (hyperbilirubinemia, prenatal/ post-natal infections, immune disorders, anoxia/ hypoxia) and/or genetic mutations (Kraus et al., 2000), whereas the late onset of the condition might be the result of other peripheral polyneuropathies. Literature has revealed that those neonates who are at the risk for developing hyperbilirubinemia and anoxia are more inclined to get ANSD (Rance et al., 1999; Akman et al., 2004; Olds & Oghalai, 2015) and also those children who

have positive family history of myelin protein zero (MPZ) gene otoferlin (OTOF) gene and peripheral myelin protein (PMP22) gene mutation with a hereditary motor sensory neuropathy (Starr et al., 2003; Varga et al., 2006). Conclusions about the underlying pathology ANSD include inner hair cell damage, disorder of the synapse or myelinisation, disorder of the auditory nerve which is accompanied with peripheral neuropathies (Starr, Sininger & Pratt, 2000).

Aetiologies of auditory dys-synchrony are just started to be noted in the literature, and found to be diverse. There are multiple aetiologies have been related with ANSD and these causative factors can be broadly classified into three i.e. transient neonatal insults, infectious conditions, and genetic factors or syndromes. Hence, it can be concluded that aetiological factors which yield to develop ANSD is found to be significantly higher in neonatal intensive care unit babies (Rea & Gibson, 2003).

1.2. Clinical features of Auditory Neuropathy Spectrum Disorder

The range of onset can fluctuate from 0 to 60 years with largest age group is showing before 2 years of age (Starr, Picton & Sininger, 1996). Based on the onset of auditory dys-synchrony it may belong to two groups: one group of patients with symptoms in infancy and other group in which symptoms develop in adolescence or early adulthood. Only 1 in 4 auditory neuropathy patients are reported to be having greater than 10 year of age as onset of symptoms (Starr et al., 2000; Sininger & Oba, 2001).

The patient's audiometric thresholds range from complete normal hearing sensitivity to profound hearing loss. Some individual might reports reduced hearing or fluctuating hearing loss, poor speech recognition especially in noisy environment but not in quite conditions (Rance et al., 2007). Most of the time, adult with ANSD might have the complaint of difficulty in discriminating speech sounds, or difficulty in understanding speech possibly due to altered temporal functioning (Starr et al., 1996). In addition, there is a higher inter-subject variability in the usage of temporal cues in the perception of speech for individuals with ANSD (Berlin et al., 2010). Literature have shown that this affects children's capability to process quickly varying acoustic signals (auditory temporal processing); which results in normal-to-severely affected speech detection as well as pure tone thresholds (Kraus et al., 2000; Rance, Cone Wesson, Wunderlich & Dowell, 2002). Further, children also reported impaired auditory processing abilities and in those situations even amplification devices such as hearing aids may not be beneficial. In addition to this the otological complaints it might be related with body temperature and climate changes (Starr, Sininger, Winter, Dereby & Oba, 1998; Starr & Rance, 2015).

1.3. Intervention of Auditory Neuropathy Spectrum Disorder

Since ANSD is a disorder of fluctuating pure tone thresholds and impaired speech perception scores, which does not correlate to the degree of hearing loss (Cone-Wesson, 2004; Wolfe & Clark, 2008), rehabilitation of ANSD exhibited as a controversy and made as a great challenge for an Audiologist (Gabr, 2016). Hence the degree of hearing loss does not have a direct relationship to the degree of dys-synchrony and could not be characterized only based on the behavioural test outcomes

(Sharma, Cardon, Henion & Roland, 2011; Swanepoel, Johl & Piener, 2013). Hence, management strategies of ANSD are not same as that of other hearing impaired children.

Children who are diagnosed to have ANSD are recommended to go for conventional amplification whenever there is a reliable degree of hearing loss which can be quantified with behavioural measures (Hayes et al., 2008). The usefulness of conventional amplification is reported to be based on the response of cortical evoked potentials and their abilities in temporal processing (Rance et al., 2002, 2004). However, when children showed poor prognosis in speech and language development even after the adequate amplification, it is better to check for cochlear implant candidacy (Attias & Raveh, 2007; Berlin et al., 2010) and its benefit is appears to be contingent on the site of the lesion. Moreover, the existence of cognitive issues associated with ANSD can also cause a delay in the threshold estimation. Hence the intervention strategies might be postponed till a consistent hearing threshold is determined which further result in delay for those children without having adequate audibility of speech sounds (Moore, Thompson & Folosom, 1992; Norton et al., 2000).

Providing hearing aids to ANSD patients (especially children) is nowadays a controversial issue (Rance, 2005) due to its arguments on the protection of cochlea and limitation in the auditory pathway. However, cochlear implantation is one of the successful rehabilitation strategies for ANSD patients with hearing impairment as well as those who have poor speech understanding (Peterson et al., 2003; Teagle et al., 2010).

1.4. Prevalence of Auditory Neuropathy Spectrum Disorder

The prevalence of ANSD in hearing impaired children is not exactly identified. Epidemiological studies concerned with prevalence of ANSD in children were very diverse from across the evaluated population and across studies (Talaat, Kabel, Samy & Elbadry, 2009; Vignesh, Jaya & Muraleedharan, 2016). There is a little knowledge regarding the prevalence of ANSD in paediatric population. Approximately 2/3rd of the ANSD individuals have no evidence of associated peripheral neuropathy, but there might be presence of peripheral neuropathy in 80% of cases >15 years of age. However, this association is commonly seen for adults and not for children. For paediatric population, the prevalence rate of ANSD approximately ranges from 5.1 to 15 per 100 in detected cases of sensorineural hearing loss (Madden, Rutter, Hilbert, Greinwald & Choo, 2002).

It was thought to be an uncommon disorder initially; however, current prevalence data showed 7 to 10% children who have permanent hearing loss are cases of ANSD (Madden et al, 2002; Rance, 2005). Researchers proposed that 1 in each 200 hearing impaired children below the age of 3.5 years (0.5%) had audiological findings which are enough to diagnose them as ANSD patients (Davis & Hirsh, 1979; Cone-Wesson & Rance, 2000). However, Berlin and his colleagues (1999) estimated that ANSD is comparatively more in those children who have permanent sensorineural hearing loss (4%).

Duman et al (2008) conducted a study on 75 school going deaf children in the age range of 6-17 year and concluded that 3 of them had ANSD (4%). Out of those children 3 children, two were not having any risk factor to develop ANSD but one got hearing impairment after vaccination as reported by the author. By considering

another school based study done by Lee and his colleagues (2001) suggested the prevalence of ANSD as 3% for 67 children of 6-12 years.

A retrospective chart which was prepared by Kirkim and his co-workers in the year 2008 based on universal newborn hearing screening program (UNHSP) outcomes for three years of Western Anatolian region of Turkey suggested the prevalence of ANSD as 15.38 % in 65 neonates of unilateral or bilateral sensorineural hearing impairment. Similar to these findings, Ngo and his colleagues (2006) also reported the prevalence of ANSD as 17.3% in all the hearing impaired neonates whoever was screened.

There was a large sample systematic study of ANSD has been carried out by Rance and his colleagues (1999) on 5199 Australian neonates who had risk for getting hearing impairment, and out of 5199, 109 children had hearing loss and 12 had ANSD which showed that approximately 1 in 9 hearing impaired neonates are reported cases of ANSD. The result displayed that in the entire population prevalence rate of hearing loss in children is 0.23% and 11.01% of them are at the risk of developing ANSD. In the screening programing conducted for neonates by Domínguez and his coleagues in the year 2007 reported that 114 neonates as having unilateral or bilateral sensorineural hearing impairment and out of this 6 had ANSD (5.26%).

In Indian scenario there are only limited studies done in different cities of India. There was a register-based retrospective study has been conducted in Mysore by Kumar and Jayaram (2006) for the data of three years considering all age groups individuals, and considered 21236 patients (11,712 males & 9524 females) to recognise the prevalence rate of ANSD. Results of their study suggested that 11205 were the diagnosed cases of permanent sensorineural hearing loss and among them 61

were the cases of ANSD i.e. 1 in 183 individuals who were suffering from ANSD (0.54%). Among the studied population there was a drastic rise in the number of ANSD cases in the age range of 13 - 18 years.

Mittal et al (2012) evaluated 487 children in the age range of 6 months to 12 years evaluated at tertiary care hospital, New Delhi. Results showed that 183 children were the identified sensorineural hearing loss cases and out of these cases, 26 of them were ANSD cases (5.3%). The have identified all those ANSD children in the age range of 3-5 years.

In another retrospective study done by Vignesh et al (2016) have assessed 2,624 cases (Male = 1,840 & Female = 784) who were in the age range of 6 month to 12 years and had a risk of developing hearing loss or with the complaint of hearing impairment. They found that out of the assessed cases, 217 (8.26 %) were the cases of sensorineural hearing loss (unilaterally or bilaterally) in different degrees and prevalence data of ANSD verified was 0.42% (N = 11) from the whole population.

Bhat, Kumar and Sinha (2007) conducted a study in Mangalore, which is a geographically located area in south India. In their study 220 school going children of 4 to 16 years (Mean age of 10 years) were considered and after the comprehensive detailed audiological evaluation of those recruited children, the prevalence of ANSD was concluded to be 2.27 %.

Table 1.1*: Prevalence of Auditory Neuropathy Spectrum Disorder (ANSD) across different studies*

Author	Study group	Prevalence of ANSD
Madden et al (2002)	Children in the age range of 1-60 months	7-10%
Rance (2005)	Children below 2 years	7-10%
Mittal et al (2012)	Children below 12 years	5.3%
Con-Wexon & Rance (2000)	Children below 3.5 years	4%
Duman et al (2008)	Children in the age range of 6-17years	4%
Lee et al (2001)	Children in the age range of 6-12years	3%
Davis & Hirsh (1979)	Children below 3.5 years	4%
Bhat et al (2007)	Children in the age range of 4-16 years	2.27%
Vignesh et al., (2016)	Infants and children (6 months -12 year)	0.42%
Ngo et al (2006)	Neonates	17.3%
Kirkim et al (2008)	Neonates	15.38%
Rance et al (1999)	Neonates	11.01%
Domínguez et al (2007)	Neonates	5.26%

The epidemiological data displayed a decrease in the prevalence of ANSD by advancing the age i.e. younger children are more prone to get ANSD compared to older children. However this can be due to an on-going process happening in ANSD i.e. some outer hair cells can be spared initially but by the progress of the condition further damage can occur or this can happen because of high gain amplification (Tallat et al., 2009).

1.5. Need for the study

Recent reports of World Health Organization (WHO) in the year 2019, found that about 466 million people across the world are having hearing impairment and out of this 34 million of them belongs to paediatric population, in which 60% of those impairment is because of preventable aetiologies. Probably by 2050, over 900 million individuals will have hearing impairment. As the prevalence rate of hearing loss increases it is essential to recognise the epidemiological data, audiological features, and connection between audiological evaluation outcomes in a clinical population like ANSD to modify the rules leading to hearing impairment and to choose suitable intervention strategies.

The prevalence of ANSD in children as mentioned in the above studies reported, mainly carried out in Western countries and there is limited information available in Indian scenario. Since there is an inadequate number of studies and ambiguity in the report about the prevalence of ANSD in India across different regions (Mittal et al reported 5.3%, Bhat et al suggested 2.27 % whereas Vignesh et al stated 0.42%) which necessitates the need for the current study. In addition, literature have shown that prevalence of ANSD in younger population are 10% (Sininger,

2002), 11% (Rance et al., 1999) and 15.4% (Kirkim, Sebertcioglu, Erdag & Ceryan, 2008). Considering the data from school going children, the prevalence of ANSD was reported as 1.5% (Lotfi & Meherkian, 2007), 2.4% (Lee et al, Mcpherson, Yuen & Wong, 2001) and 4% (Duman et al., 2008). These epidemiological findings can be concluded in a way that younger population is more affected compared to older children which again indicates need for having prevalence studies in both younger and older children.

As the range of functional abilities is diverse, due to the uniqueness of the condition the audiological, speech and language intervention of ANSD is challenging in infants and children. Moreover the progressive impact of ANSD cannot be identified only with the auditory findings. Children who are diagnosed as having ANSD require audiological as well as educational management which probably needs more attention compared to those children who have hearing loss in general. Due to this fact screening for ANSD might be appropriate not only in hospitals but also in schools.

In All India Institute of Speech and Hearing (AIISH), a large number of children in the age range of 0- 12 years reported with hearing loss in every year, and ANSD can be one of the conditions which might be observed in these reported cases. Hence it is necessary to document the information about the epidemiological details and find out the prevalence of ANSD in these reported cases of hearing loss at AIISH.

1.6. Aim of the study

The aim of the study was to estimate the prevalence of ANSD in children in the age range of 0-12 years reported at All India Institute of Speech and Hearing, Mysuru, between 1st January 2018 to 31st December, 2018.

1.7 Objectives of the study

1. To estimate the total number of sensorineural hearing loss cases in children reported at All India Institute of Speech and Hearing, Mysuru, between 1st January 2018 and 31st December 2018 using a register based information.
2. To estimate the prevalence of ANSD among those cases reported with sensorineural hearing loss in the age range of 0-12 years.

Chapter 2

Method

The current study was aimed to estimate the prevalence of auditory neuropathy spectrum disorder in children in the age range of 0-12 years (mean age of 6 years) reported at All India Institute of Speech and Hearing (AIISH), Mysuru between 1stJanuary 2018 and 31st December 2018. To meet the above aim, below mentioned method was adopted.

2.1. Participants

A retrospective study was executed by reviewing the case files of 1147 children (621 males & 526 females) visited at All India Institute of Speech and Hearing (AIISH), Mysuru between 1stJanuary 2018 and 31st December 2018, to estimate the one year prevalence of ANSD in children. The Out Patient Department (OPD) register was used to obtain the total number of cases and demographic details (age, gender, socio-economic status), medical history (prenatal, perinatal, & postnatal history), family history, developmental history, educational history, otologic complaints, otolaryngological evaluation results, comprehensive audiological evaluation outcomes, speech and language evaluation findings and neurological evaluation details of those children reported during the above mentioned 12 months of time period.

2.1.1. Participant inclusion criteria

Those children who underwent the complete audiological assessment and final provisional diagnosis were reported in the case files, were only included in the study.

All these infants and children have undergone either Behavioural observation audiometry (BOA)/ Visual reinforcement audiometry (VRA)/ Conditioned play audiometry(CPA)/ Pure tone audiometry (PTA), Immittance audiometry (Tympanometry & Reflexometry), Otoacoustic emissions (TEOAE/ DPOAE) and click evoked auditory brainstem responses (ABR) using the standard protocol for each test.

1) Normal tympanometric findings (Static admittance: 0.35 to 0.9 mmho; Ear canal volume: 0.5 to 1.5 cc; Peak pressure: +50 to -50 daPa as per Van Camp, Margolis, Wilson, Creten & Shranks, 1986)
2) Preserved cochlear functioning (Transient evoked otoacoustic emissions/ Distortion product otoacoustic emission or identifiable cochlear microphonic.
3) Altered auditory nerve responses (Abnormal or absent ABR).

2.2 Procedure

All the case files of children reported at AIISH during the above mentioned 12 months period was considered for the study by retrieving their case numbers. As per the inclusion criteria, those children who were diagnosed to have sensorineural hearing loss including auditory neuropathy spectrum disorder were considered and the information was taken to identify its one year prevalence. It was determined from the case files that all the children had been examined using a standardised test battery which includes both the behavioural tests and objective tests.

2.2.1. Behavioural evaluation

Assessment was initiated with an otoscopic examination which evaluates the status of the external ear and tympanic membrane followed by the behavioural evaluation (BOA/VRA/CPA/ PTA) which was accomplished using a calibrated dual channel audiometer in a sound treated room under standard conditions. An audiological test is selected based on the age of the child such as Behavioural Observational Audiometry (BOA) for infants lesser than 6 months of age (ASHA, 2004), Visual Reinforcement for children of 5 to 6 months and 36 months (Suzuki & Obiga, 1960), Conditioned play audiometry for children of 3-6 years (Madell, 1998) and Pure tone audiometry for children older than 6 years.

2.2.2 Objective Evaluation

Objective tests include tympanometry for a 226 Hz probe tone and acoustic reflex test includes both ipsilateral and contralateral testing at frequencies of 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz had been performed using a calibrated middle ear analyser.

Transient evoked otoacoustic emissions were recorded in a sound proof room for click stimulus at 80 dBPeSPL. A response was measured to be normal whenever the reproducibility was more than 75%, and the overall signal-to-noise ratio (SNR) was greater than 6 dB SNR at least for three consecutive frequencies (Norton et al., 2000).

Click evoked auditory brainstem response (ABR) testing had been performed to check the integrity of the auditory system. Absolute latency (Wave I, III & V), morphology and amplitude of responses were noted down. Whenever there was a

presence of Cochlear Microphonic (CM) while recording ABR the polarity was altered (both condensation & rarefaction) to confirm its presence. Table 1.2 depicts the protocol of stimulus and acquisition parameters for click evoked auditory brainstem response testing which was similar for all children.

Table 2.1*: Protocol used for auditory brainstem response (ABR) testing*

Stimulus parameters	Acquisition parameters
Stimulus: Clicks	Filter setting : 30 Hz to 1500 Hz
Duration 100 µs	Montage : Cz-A1 and Cz-A2
Polarity : Rarefaction	Rate : 11.1/s
Presentation level : 90 dB nHL	Analysis window : 10 ms
Transducer: Inserts (ER- 3A)	Artifact rejection above : 50 uV
Number of sweeps : 2000	Electrode Montage : Non inverting - Cz, Inverting-M1, Reference-M2

While reviewing the case files all the risk factor which yields to hearing loss were also noted down. The risk factors includes positive family history of hearing loss, TORCH infections (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes Simplex & Others), Preterm delivery (<34 weeks of gestational age), Low birth Weight (<1.5 kg), Hyperbilirubinemia, Meningitis, Cranio-facial anomalies, Neonatal intensive care more than 7 days, Mechanical ventilation for more than of 5 days, Ototoxic medication and Syndromes associated with hearing loss.

2.3. Statistical analysis

Descriptive statistics was carried out to estimate total number of children with and without hearing loss. Further, it was also analysed among children with hearing loss having different degree, and type of hearing loss. In sensorineural hearing loss, the number of children diagnosed as ANSD was identified and the prevalence of ANSD was estimated as per the registered total number of cases during one year period (from 1st January 2018- 31st December 2018).

Chapter 3

Results

The present study involved retrospective analyses of the case files of children with or without hearing loss reported at All India Institute of Speech and Hearing (AIISH), Mysuru between 1st January 2018 and 31st December 2018. Out of 1180 children, 1147 case files of children in the age range of 0 to 12 years (mean age of 6 years) were reviewed as the remaining case files were not available for review at the time of study.

3.1. Prevalence of hearing impairment in children (0-12 years)

Out of 1147 children, 995 children with hearing loss (427 Female & 568 Male) were identified whereas only 152 children (97 Female & 55 Male) were identified as having normal hearing. For the analysis of prevalence of hearing impairment with respect to different type of hearing loss such as conductive hearing loss (CHL), mixed hearing loss (MHL) and sensorineural hearing loss (SNHL), the data were considered individually. In the present study, there were 747 children (65.13%) with sensorineural hearing loss (420 Male & 327 Female); 155 children (13.51%) with conductive hearing loss (90 Male & 65 Female), and only 93 children (8.11%) who were diagnosed as mixed hearing loss (56 Male & 37 Female). Hence, prevalence of hearing loss in terms of type of hearing loss showed the trend of having higher prevalence for sensorineural hearing loss followed by conductive hearing loss and the lowest prevalence is for mixed hearing loss. The prevalence of hearing impairment in children as type of hearing loss is depicted in Figure 3.1.

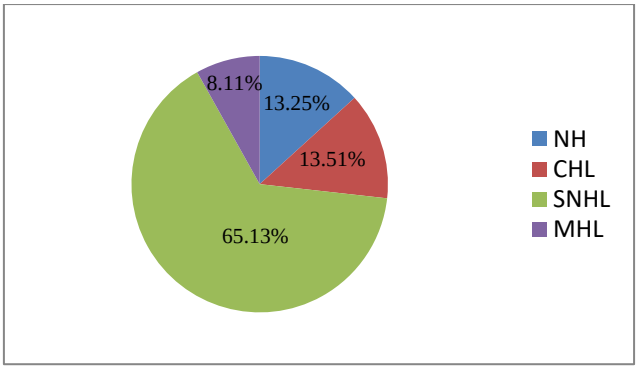

Figure 3.1: Prevalence of hearing impairment in children *(NH: Normal hearing; CHL: Conductive hearing loss; SNHL: Sensorineural hearing loss; MHL: Mixed hearing loss)*

3.2. Prevalence of Auditory Neuropathy Spectrum Disorder in children

Eight out of 995 hearing impaired children were identified to have ANSD following the inclusion criteria of the current study which shows that 1 out of 124 had ANSD (0.8%). However, the prevalence of ANSD is 1 out of 93 (1.07%) when only children with permanent sensorineural hearing loss are considered (Figure 3.2)

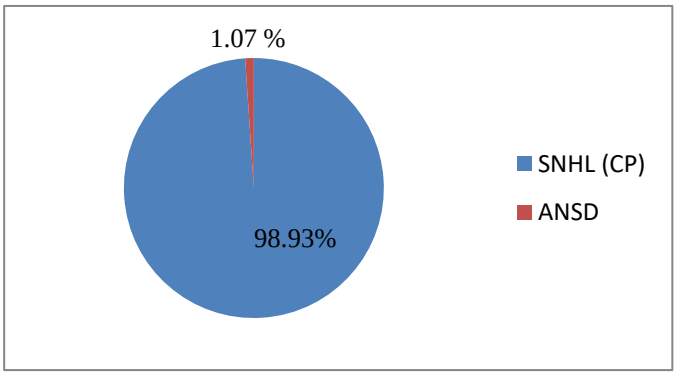

Figure 3.2: Prevalence of ANSD in children *(SNHL: Sensorineural hearing loss; CP: Cochlear pathology; ANSD: Auditory neuropathy spectrum disorder)*

3.3. Gender Difference in ANSD children

The prevalence of ANSD with respect to gender suggested that, out of 8 ANSD children, only 2 children (25%) were females and 6 (75%) were males. The gender differences among ANSD children indicate that males have three times higher in prevalence compared to females in the age range of 0 to 12 years (Figure 3.3).

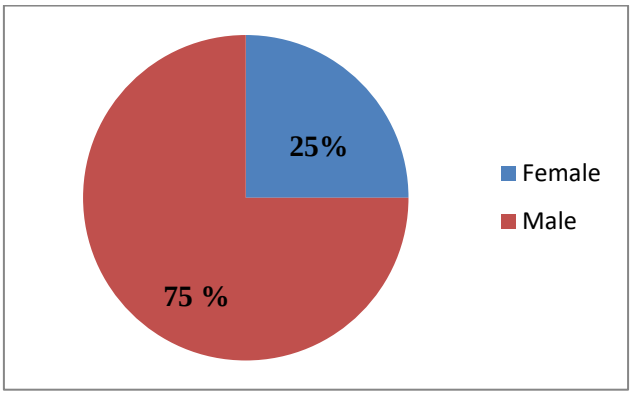

Figure 3.3: Gender difference in ANSD

3.4. Audiological Evaluation outcomes of children with ANSD

Pure tone Audiometry evaluation showed out of 8 children with ANSD, 7 children had bilateral symmetrical hearing loss. However, there was no particular audiogram configuration traced out due to their younger age participation. The degree of hearing loss among reported ANSD children had ranges in between mild-to-severe. Table 3.1 shows the number of ANSD children with different degree of hearing impairment.

Table 3.1*: Number of ANSD children with different degree of hearing impairment*.

Degree of Hearing Impairment	Number of children
Minimal hearing loss	1
Mild hearing loss	1
Mild-to-moderate hearing loss	1
Moderate hearing loss	1
Moderately severe hearing loss	1
Severe hearing loss	2

Immittance evaluation was performed on all children identified with ANSD using 226 Hz probe tone. Tympanometry showed 'A' type tympanogram in 4 children and 'As' type tympanogram for another 4 children with absent ipsilateral and contralateral stapedial reflexes at all the frequencies which were tested (500 Hz, 1000 Hz, 2000 Hz & 4000 Hz). *Transient evoked otoacoustic emissions (TEOAEs)* were used to evaluate the functioning of the outer hair cells and it was present bilaterally for 7 ANSD children at 80 dB PeSPL except one child.

Click evoked Auditory brainstem response was done to assess the integrity of the functioning of auditory nerve in ANSD children. Results showed none of the children had identifiable peaks for click evoked ABR in both the ears at 90 dBnHL. While recording click evoked ABR, the presence or absence of *cochlear microphonic* was also looked upon, as mentioned in the report. It was noticed that there were presence of cochlear microphonic in all the reported ANSD children except one child. The presence of cochlear microphonic was confirmed by inverting the polarity of the stimulus while recording clicked evoked ABR. The comprehensive audiological finding of ANSD children along with risk factors as reported and documented in case files is illustrated in Table 3.2.

Table 3.2*: Demographic details, audiological finding and risk factors of ANSD children*

Case No.	AGE (Year)	GENDER	EAR	Degree of HL (BOA/VRA/CPA/PTA)	TYMP	REFLEX	TEOAE	Click evoked ABR	CM (ms)	RISK FACTORS
1	8	M	RE	Moderately severe HL	A	Absent	Present	Absent	3	Neonatal jaundice, Blood transfusion, NICU-5 days
			LE	Moderately severe HL	A	Absent	Present	Absent	3	
2	3	M	RE	Mild HL	A	Absent	Present	Absent	2	Neonatal jaundice, NICU-5 Days
			LE	Moderate SNHL	A	Absent	Present	Absent	2	
3	6	F	RE	Mild SNHL	As	Absent	Present	Absent	4.5	Sibling history (Sister is HI), Preterm, LBW, Neonatal jaundice, Phototherapy, NICU - 10 Days
			LE	Mild SNHL	As	Absent	Present	Absent	3.2	
4	9	F	RE	Severe HL	A	Absent	Present	Absent	Nil	Consanguity (first degree), Excessive vomiting till 9 months
			LE	Severe HL	A	Absent	Present	Absent	Nil	
5	12	M	RE	Minimal HL	A	Absent	Present	Absent	2	NIL
			LE	Minimal HL	A	Absent	Present	Absent	2	
6	7	M	RE	Moderate SNHL	As	Absent	Absent	Absent	2.05	Neonatal jaundice, NICU-124Days
			LE	Moderate SNHL	As	Absent	Absent	Absent	3.13	
7	1	M	RE	Mild to moderate SNHL	As	Absent	Present	Absent	3.11	Neonatal jaundice, Blood transfusion, NICU-5 days
			LE	Mild to moderate SNHL	As	Absent	Present	Absent	1.78	
8	3	M	RE	Severe HL	As	Absent	Present	Absent	2.5	Neonatal jaundice, NICU-12Days
			LE	Severe HL	As	Absent	Present	Absent	2.51	

M: Male; F: Female; RE: Right Ear; LE: Left Ear; HL: Hearing loss; SNHL: Sensorineural hearing loss; ms: Millisecond; NICU: Neonatal Intensive care Unit

The *high risk factors* associated with these ANSD children were found to be neonatal jaundice, preterm delivery, low birth weight, positive family history, sibling history and neonatal intensive care more than 5 days as shown in Table 3.2. Six out of 8 ANSD children had the history of neonatal jaundice (75%) and underwent phototherapy for the same and had neonatal intensive care more than 5 days. There was only one child with ANSD (Case 3) reported as preterm baby and had low birth weight (12.5%). Similarly, only one child with ANSD (Case 4) had positive family history of hearing impairment (12.5%). Out of 8 ANSD children, there was only one child (case 5) reported no significant high risk factors associated with ANSD (12.5%). The major risk factors among these 8 children with ANSD are depicted in Figure 3.4

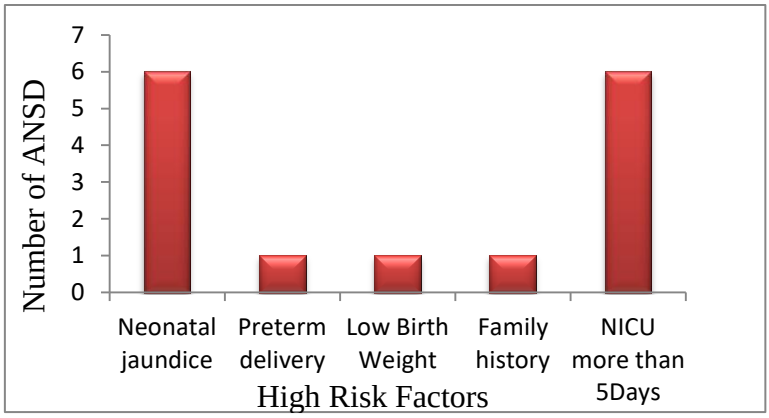

Figure 3.4: High Risk factors for ANSD

Chapter 4

Discussion

The purpose of the current study was to estimate the prevalence of Auditory Neuropathy Spectrum Disorder in children in the age range of 0 to 12 years (mean age of 6 years) reported at All India Institute of Speech and Hearing (AIISH) Mysuru between 1st January 2018 and 31st December 2018. The study also reported the total number of children with sensorineural hearing loss identified at the Department of Audiology during the above mentioned time period.

4.1. Prevalence of Auditory Neuropathy Spectrum Disorder

Eight out of 995 hearing impaired children were identified to have auditory neuropathy spectrum disorder following the inclusion criteria of the current study, which shows that 1 out of 124 children with hearing loss had ANSD. Hence, the prevalence of ANSD is 0.8% among children with hearing loss up to 12 years of age in the present study. However, the prevalence of ANSD is 1.07%, when only children with permanent sensorineural hearing loss are considered i.e. 1 out of 93 children with SNHL. The results of the current study are in agreement with the existing literature (Madden et al., 2002; Mason, Michele, Stevens, Ruth & Hashisaki, 2003; Tang, Mc Pherson, Yuen, Wong & Lee, 2004; Kirkim et al., 2008; Kumar & Jayaram, 2006; Penido & Isaac, 2013; Vignesh et al., 2016). The prevalence rate of 1.07 % in the current study correlates with the findings of 3 year data described by Penido and Isaac (2013) which is approximately 1.2% in subjects with sensorineural hearing loss in the age range of 0- 95 years. Similarly study done by Kumar and Jayaram (2006) have

stated prevalence of ANSD as 0.54%, i.e. for 1 in 183 individuals consisted of children, adults and elderly population. The prevalence of ANSD reported by Kumar and Jayram (2006) as well as Penido and Isaac (2013) had analysed the data of 3 years and included all age groups whereas present study only reported one year data of children up to 12 years. Hence, there may be differences in the prevalence of ANSD could be because of inclusion of the population in the above mentioned studies.

In contrast with the present study, few studies reported higher prevalence of ANSD in children (Davis & Hirsh, 1979; Rance et al., 1999; Con-Wexon & Rance, 2000; Lee et al., 2001; Duman et al., 2008). A retrospective study done in children in the age range of 6 months to 12 years by Vignesh et al (2016) in Tamilnadu, India and reported prevalence rate of ANSD as 0.42% when overall population was considered whereas when only SNHL children were considered the prevalence of ANSD reported is 5.06%. The prevalence of ANSD reported in the Vignesh et al study is different compared to present study could be due to sample size difference between the two studies along with other factors such as geographical region and temperature variation between the two population (Varga et al., 2006; Marlin et al., 2010; Starr & Rance, 2015). Similarly Mittal et al (2012) has described the prevalence of 5.3% in 487 sensorineural hearing loss children below 12 years of age. By considering all these results including the present study the variability in findings of prevalence rate could be because of regional variation. Hence, understanding the regional zone in terms of its climate variation is important since there are reported cases of temperature sensitive forms of ANSD (Starr & Rance, 2015).

4.2. Gender Difference in ANSD children

The exact information regarding the gender difference is poorly understood till date. The prevalence of ANSD in the present study with respect to gender suggested that more number of males i.e. 75% with ANSD in comparison to females i.e. 25%, which indicates that males are more prone to get ANSD compared to females among children. Certain study findings reported equal gender contribution for ANSD (Sininger & Oba, 2001) at the same time there are literature recommends male dominancy in prevalence of ANSD (Raveh, Buller, Badrana & Attias, 2007; Duman et al., 2008). However, literature could not reveal the exact reason for male dominancy in ANSD. One of the observations pointed out in the current study was that total number of hearing impaired male children was higher compared to females.

Contrary to these findings other studies recommended the female-to-male ratio as 2:1 in ANSD (Kumar & Jayaram, 2006). In consensus with this Penido & Isaac (2013) and Narne and his co-workers (2016) also recommended the higher prevalence rate of ANSD in female participants could be because of hormonal changes at the time of pubertal age which are observed similarly in few other studies (Jijo & Yathiraj, 2012; Chandan & Prabhu, 2015).

4.3. Evaluation outcomes of children with ANSD

All the hearing impaired children who were identified as having ANSD were bilateral (100%) in the current study. Many of the reports recommended the presence of bilateral ANSD (Madden et al., 2002; Raveh et al., 2007). However, there are unilateral ANSD cases reported in the literature which is accounting lesser than 10%

among all the ANSD's. The unilateral ANSD can be the result of congenital malformation of cochlear nerve either partially (hypoplasia) or completely (aplasia) (Buchman et al., 2006; Laury, Casey, McKay & Germiller, 2009; Liu, Bu,Wu &Xing, 2012). In the current study none of the children had cochlear nerve malformation as revealed by the neurological evaluation findings. Hence, present study reported only bilateral ANSD cases.

There was no particular audiogram configuration which was noted in all the children with the behavioural tests as they had inconsistent response or were not cooperative during the evaluation. However, those children who performed for the evaluation also haven't had any particular audiogram configuration. The audiological features of the hearing impairment showed varying degree from mild-to-severe. In agreement with present findings, there is existing literature regarding the degree of hearing impairment (Kumar & Jayaram, 2006; Vignesh et al., 2016). This relates with the outcomes of Starr et al (1996) which displays in 80% of their patients diagnosed with ANSD, their major issue was reduced hearing sensitivity.

Immittance evaluation showed either 'A' or 'As' tympanogram for 226 Hz Probe tone with absent ipsilateral and contralateral stapedial reflex for all the frequencies which were tested (500 Hz, 1000 Hz, 2000 Hz & 4000 Hz). These findings approximate with the outcomes of the work done in literature which displays bilateral ANSD with 'A' or 'As' tympanogram with absent acoustic reflexes (Madden et al., 2002; Rance, 2005; Berlin et al., 2010; Starr & Rance, 2015; Vignesh et al., 2016). The abnormality in the middle ear muscle reflex is due to asynchronous firing of the auditory nerve fibres (Berlin et al., 2010).

Transient evoked otoacoustic emissions were present bilaterally for 7 children at 80 dBPeSPL except for one child. Similarly *Cochlear microphonic* was also present bilaterally in 7 children except for one child. These results showed the conserved cochlear functioning in diagnosed children with ANSD. The exact reasons for absence of OAE response were not known in one child. However, there is reported literature about absence of OAEs in ANSD children (Deltenre, Mansbach, Bozet, Clercx & Hecox, 1997; Rance et al., 1999; Starr et al., 2001; Tang et al., 2008). This can be due to history of prior middle ear disorders such as infection, and Eustachian tube dysfunctions. These children can pass the screening with tympanometry but there could be attenuated or completely absent cochlear hair cell response having both conductive hearing loss and impaired auditory nerve functioning together (Starr et al., 2001; Tang et al., 2008). Hence, those children could be diagnosed with their disproportionately in poor speech perception scores and electroacoustic and electrophysiological test outcomes.

Click evoked auditory brainstem response was not detectable or repeatable for all the eight ANSD children bilaterally. It shows severe dys-functioning of auditory nerve in ANSD children. These findings are consensus to the existing literature regarding the auditory evoked potentials in ANSD (Rance et al., 1999; Talaat et al., 2009; Midgley, 2013). Still, an absent ABR did not essentially indicate the presence of severe or profound hearing loss, so it is mandatory to differentially diagnose auditory maturation delay and ANSD with the subsequent follow up evaluations.

Risk Factors associated with ANSD which yields to ANSD were found to be neonatal jaundice, preterm delivery, low birth weight, positive family history, sibling history and neonatal intensive care more than 5 days. Six out of 8 ANSD children had the history of neonatal jaundice, underwent phototherapy for the same and had

neonatal intensive care more than 5 days; 1 out of 8 ANSD children had premature delivery, low birth weight and positive family history of hearing impairment. In consensus with the current findings literature also suggested certain aetiological factors such as neonatal jaundice, premature delivery, birth asphyxia, perinatal infections (Mumps, Toxoplasmosis, Meningitis, & Encephalitis), consanguinity, ototoxic drug usage, cerebral palsy and/or genetic factors plays a major role in these pathological defect development (Zdanski, Buchman, Rousch, Teagle & Brown, 2004; Kirkim et al., 2008; Foerst et al., 2006; Raveh et al., 2007). In support to the present study outcome it is recognised that hyperbilirubinemia can result in permanent as well as temporary auditory pathways dysfunction (Kirkim et al., 2008; Kumar & Jayaram, 2006). In contrast to these findings there are literature reports which suggested no observable risk factors to develop ANSD (Lee et al., 2001; Raveh et al., 2007; Duman et al., 2008). In the present study while for one child there was no risk factors reported prenatally, perinatally or postnatally in order to develop ANSD.

Chapter 5

Summary and conclusion

The present study was aimed to estimate the prevalence of ANSD in children up to 12 years of age evaluated at All India Institute of speech and Hearing during 1st January and 31st December 2018. Retrospective register based study was carried out by retrieving the case numbers and investigating the available information regarding each child and case files were segregated into groups based on their type of hearing losses. From the current study it can be concluded that 8 out of 995 hearing impaired children were identified to have ANSD following the inclusion criteria of the current study, which shows that 1 out of 124 children with hearing loss had ANSD (0.8%). However, the prevalence of ANSD is 1.07%, when only children with permanent sensorineural hearing loss are considered (1 in 93 children with SNHL). These findings recommended that even though ANSD was thought be a rare disorder initially, it is not currently which can be stated based on the existing literature.

5.1. Clinical implication

1. The present study will be helpful in having knowledge regarding the prevalence of ANSD in paediatric population (age range of 0-12 years) in Indian context.
2. The documented data will be useful in developing appropriate management strategies for children with ANSD.
3. Add information to the existing literature.

Chapter 6

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