DISTORTION PRODUCT OTOACOUSTIC EMISSIONS INPUT- OUTPUT FUNCTION IN INDIVIDUALS WITH AUDITORY NEUROPATHY SPECTRUM DISORDER

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April, 2018

CERTIFICATE

This is to certify that this dissertation entitled "**Distortion Product Otoacoustic Emissions Input- output function in individuals with Auditory Neuropathy Spectrum Disorder**" bonafide work submitted in part fulfillment for the degree of Master of science (Audiology) of the student (Registration No: 16AUD009). This has been carried out under the guidance of a faculty of this institute and has not been submitted earlier to any other university for the award or any other diploma or degree.

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This is to certify that this dissertation entitled "**Distortion Product Otoacoustic Emissions Input- output function in individuals with Auditory Neuropathy Spectrum Disorder**" has been prepared under my supervision and guidance. It is also certified that this has not been submitted earlier to any other university for the award or any other Diploma or Degree.

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DECLARATION

This is to certify that this dissertation entitled **"Distortion Product Otoacoustic Emissions Input- output function in individuals with Auditory Neuropathy Spectrum Disorder"** is the result of my own study under the guidance of Dr. Prashanth Prabhu P., Lecturer in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysuru and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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Dedicated to my Parents, Brother, and Kitty…

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Abstract

Auditory Neuropathy Spectrum Disorder (ANSD) is a disorder characterized by the absence of acoustic Reflex, absent or abnormal auditory brainstem response, poor speech perception scores and the presence of otoacoustic emissions. This had led to the widespread belief that cochlear functioning is normal or more or less unaffected in these individuals. But recent studies have reported finding differences in the spectral distribution and amplitude of otoacoustic emissions in individuals with ANSD. This study attempted to compare the slope and area of distortion product otoacoustic emissions input output (DPOAE I/O) functions between a normal control group and individuals with ANSD. It was also investigated if there was any correlation between the slope and area of the DPOAE I/O function and hearing loss and speech identification scores. Our findings revealed that there was a significant difference between the DPOAE I/O slope and area in the lower frequency regions (1 kHz, 1.5 kHz and 2 kHz). There was no correlation found between slope, area and hearing loss and speech identification score. This is probably due to the hearing loss being a result of inner hair cell damage and speech identification scores being affected by disrupted temporal function of the auditory nerve, while OAEs are a product of outer hair cell functioning. It has been reported that slope and area of DPOAE I/O function are a direct representation of cochlear health. Therefore, it can be stated that there may be some subtle pathology at the level of the cochlea in individuals with ANSD.

Chapter 1

INTRODUCTION

Auditory Neuropathy Spectrum Disorder (ANSD) is an electrophysiological diagnosis that is reached when test results indicate the presence of Evoked Otoacoustic Emission (OAEs), cochlear microphonics, absent or abnormal Evoked Auditory Brainstem Responses, absent Stapedial reflex and variable behavioral hearing thresholds (Starr, Picton, Sininger, Hood, & Berlin, 1996). It is sometimes also referred to as, Auditory Neuropathy (AN), owing to a great difference in the possible pathologies or as Auditory Dys-synchrony (AD) (Berlin, Hood, Morlet, Rose, & Brashears, 2003). The earliest reports of ANSD were documented in the 1970s (Hinchcliffe & Osuntokun, 1972). More cases were encountered again in the 1980s when patients presenting with normal pure tone audiograms and absent auditory brainstem responses were noted, along with a difficulty in understanding speech (Manchaiah, Zhao, Danesh, & Duprey, 2011). These have now been found to be a common indicator of ANSD, although a wide variation in the degree of hearing losses, from mild to severe can be present. Also, OAEs are usually preserved or of higher amplitude in them, mostly a result of impaired functioning of the efferent suppression (Berlin et al., 2003; Teagle et al., 2013).

In India, the prevalence of ANSD is 5.3% of the pediatric population in tertiary care hospitals, and 14% in those diagnosed with severe to profound hearing loss (Mittal et al., 2012). The prevalence of ANSD in children with hearing impairment going to school is reported to be about 2.47 % (Bhat, Kumar, & Sinha, 2007). In addition, Kumar

& Jayaram (2006), reported a prevalence of ANSD as 1 in 183 in clients diagnosed as having Sensorineural hearing loss.

Even though a lot of research has been dedicated to finding the specific etiology of ANSD, the results remain more or less inconclusive. It has been reported by Manchaiah et al., (2011) that the largest proportion of ANSD is due to genetic factors that can be syndromic, mitochondrial related or non-syndromic. Mostly, ANSD is attributed to dysfunction at the inner hair cells, the junction of the spiral ganglion cells and/or the auditory nerve (Amatuzzi, Liberman, & Northrop, 2011; Nachman, 2012; Rohr, 2011). But, since OAEs are usually present and robust in these individuals despite the variation in etiologies, otoacoustic emissions (OAEs) are routinely used clinically to assess cases of ANSD, having proven to be a valuable diagnostic tool (Berlin et al., 2010).

OAEs are pre-neural phenomenon that occurs at the level of the cochlea. Distortion Product OAEs (DPOAEs) are produced when two tones interact on the basilar membrane. With greatest amplitude of the response is at around the 2f1-f2 frequency, where f1 and f2 are the two frequencies that are presented simultaneously to the same ear (Lonsbury-Martin & Martin, 1990). DPOAEs are dependent on the level of presentation of these tones, and an I/O or input-output function can be obtained by keeping the stimulus frequency and frequency ratio constant. Through this, audiometric thresholds can be estimated in clients who may be incapable of responding to behavioral tests. The relation between these two measures becomes stronger depending on the frequency of the signal [reviewed in (Rasetshwane, Neely, Kopun, & Gorga, 2013; Rasetshwane et al., 2015)] and when repeated estimates are combined in a multivariate analysis. The input-

output function slope obtained for different input levels, is directly reliant on cochlear health and therefore gives a picture of the supra-threshold nonlinear characteristics of the cochlea.

1.1 Need for the study

Auditory Neuropathy Spectrum disorder has often been attributed to dysfunction at either the inner hair cells in the cochlea, the synapse between the IHCs and the auditory nerve, at the spiral ganglion, due to demyelination of the auditory nerve, or a depletion of neuronal populations in the brainstem (Rance & Barker, 2009). Traditionally, cochlear functioning is reported to be normal in individuals with ANSD. However, there are studies which report that the properties of OAE are different in individuals with ANSD compared to normal control. A study by Kumar, Avilala, Mohan and Barman (2012), compared Spontaneous Evoked Otoacoustic Emissions (SOAEs) between a group of normal hearing listeners and a group of individuals with acquired ANSD. It was found that SOAEs show a different spectral distribution (<1.5 kHz) in the clinical group versus the normal control group (>1.5 kHz), along with greater numbers of multiple SOAEs. These changes were attributed to subtle impairment in the functioning of the cochlea and the medial olivocochlear system. In another study by Narne, Prabhu and Chatni (2014) time frequency analysis of Transient Evoked Otoacoustic Emissions (TEOAEs) was done. They compared findings between individuals with ANSD and a normal group using wavelet transform method. Higher amplitude TEOAEs, with slightly shorter latencies for lower frequency signals than the normal control group were found in

the clinical group, which were also thought to be caused by damage to the efferent system.

Thus, the above studies suggest that there could be a subtle cochlear impairment in individuals with ANSD. There are no studies which have attempted to explore the differences in cochlear non-linearity, if any, in individuals with ANSD. It is well reported that DPOAE input-output function can explore the changes in cochlear functioning. Also, the slope of DPOAE I/O function is a test of cochlear non-linearity, which is unexplored in individuals with ANSD (Campos et al., 2011). It has been stated that area of DPOAE I/O is a more robust measure of cochlear non-linearity than a single slope measure (Gates, Mills, Nam, D 'agostino, & Rubel, 2002). Thus, the present study attempts to investigate the differences DPOAE input-output function (in terms of slope and area) between individuals with normal hearing and ANSD. It is also attempted to study these differences, if any across different frequencies. In addition, it is also attempted to correlate the results of DPOAE input-output function with pure tone average and speech identification scores in individuals with ANSD. Hence, the study would help in exploring and understanding the pathophysiology of ANSD.

1.2 Aim of the Study

The aim of the study is to evaluate distortion product otoacoustic emissions input-output function in individuals with auditory neuropathy spectrum disorder.

1.3 Objectives of the study

- To compare the slope of DPOAE input/output (DP I/O) between individuals with normal hearing and ANSD.
- To compare the area under DP I/O between individuals with normal hearing and ANSD.
- To study the effect of frequency on DP I/O slope and area of DP I/O in both the groups.
- To correlate the slope of DP I/O and area of DP I/O with pure tone average and speech identification scores in individuals with ANSD.

1.4 Null Hypotheses

- There is no significant difference in the slope of DPOAE input/output (DP I/O) between individuals with normal hearing and ANSD.
- There is no significant difference in the area under DP I/O between individuals with normal hearing and ANSD.
- There is no significant difference in the effect of frequency on DP I/O slope and area of DP I/O in both the groups.
- There is no significant relationship between the slope of DP I/O and area of DP I/O with pure tone average and speech identification scores in individuals with ANSD.

Chapter 2

REVIEW OF LITERATURE

2.1 Auditory Neuropathy Spectrum Disorder

Although cases matching the symptoms of Auditory Neuropathy were reported as early as the 1970s, initially reported by (Hinchcliffe, Osuntokun,& Adeuja, 1972), it was specifically referred by this term in the 1990s (Starr, Picton, Sininger, Hood, & Berlin, 1996) where a group of individuals with hearing deficits who have preserved otoacoustic emissions and absent or severely abnormal auditory brainstem responses were identified. Since the OAEs were present, the cochlea was normal, with a disorder of the functioning of the auditory nerve, which may be caused by a "neuropathy" that may occur on its own or be a part of some generalized neuropathic process.

Since then, there has been a lot of discussion regarding the most the proper term for this disorder, as there have been many different pathologies that lead to it, and they may wary among individuals. Some have chosen to call it Auditory Dys-synchrony (Berlin et al., 2002), others prefer the term Auditory Neuropathy. Then, in 2008 at a panel convened in Como, Italy, for the development of guidelines for the management and identification of infants with Auditory Neuropathy, it was decided that the disorder would be referred to as Auditory Neuropathy Spectrum Disorder to account for the variations in its nature. (Guidelines Development Conference on the Identification and Management of Infants with Auditory Neuropathy, International Newborn Hearing Screening Conference, Como, Italy, June 19-21, 2008).

2.2 Prevalence of Auditory Neuropathy Spectrum Disorder

In general, the incidence rate of ANSD is reported to be around 11% to 1.83% of the hearing impaired population, (Rance et al., 1999). It was found to be present in 1 out of 200 children with hearing loss (Davis & Hirsh, 1979). Berlin et al. (1999) estimated that ANSD is present in at least 4% of children with permanent hearing loss, and among infants diagnosed with sensorineural hearing loss, the prevalence was 5.1% (Bielecki, Horbulewicz, & Wolan, 2012). The prevalence rates increase up to 40% in hearing impaired NICU patients (Rea & Gibson, 2003). Approximately equal distribution was found between males and females, prevalence being 55% and 45% respectively (Sininger & Starr, 2001).

In India, the prevalence of ANSD in school age children (between grade one and grade 8), was found to be 2.27% (Bhat et al., 2007), and therefore it is not considered a very rare disorder. It was reported in a later study that 1 in 183 individuals with Sensorineural hearing loss had ANSD (Kumar & Jayaram, 2006), with the female to male ratio being 2:1.The prevalence in the pediatric population in tertiary care hospitals is estimated to be 5.3%, and as high as 14% in those diagnosed with severe to profound hearing loss (Mittal et al., 2012). Similar findings were obtained in a retrospective study by Vignesh, Jaya and Muraleedharan (2016), where out of 217 children with sensory neural hearing loss, 5.06 % (N = 11) had ANSD.

2.3 Onset of ANSD

The onset of ANSD has been reported to be anywhere from birth to sixty years of age. There seem to be some differences in the mean age of onset between countries, with the west showing an earlier onset with the majority showing an onset before age two, and 75% of the patients seen being below age ten when the symptoms first began (Berlin et al., 2010; Sininger & Starr, 2001), while in India, the onset was found to be a little later on. A study by Kumar and Jayaram (2006), shows that the mean age of onset is 16 years in the Indian scenario, with 59% of the cases showing symptoms between age fourteen and early twenty four. In adults, late-onset ANSD has been reported in some conditions such as exposure to xylene (solvent) (Draper & Bamiou, 2009). In a study by Prabhu, Avilala and Manjula (2012), late-onset ANSD is found in individuals with certain pre-disposing factors such as low economic status, exposure to toxic substances, a family history of ANSD.

2.4 Pathophysiology of ANSD

As established earlier, ANSD has a multitude of etiologies and varies between individuals, but mostly the common sites of lesion are insults to the cochlear inner hair cells (IHCs), an abnormality of inner hair cells or of auditory nerve fiber synapse, a spiral ganglion cell disorder, a depletion of neuronal populations in the auditory brain stem, and demyelination of the auditory nerve (Rance, McKay, & Grayden, 2004).

2.4.1 Cochlear inner hair cell dysfunction and loss

The inner hair cells form a crucial part of the hearing mechanism. The problems affecting the dendritic nerve terminals have objective findings that are similar to those of ribbon synapse disorders, (normal inner hair cell functions and an absence of compound action potentials in the nerve responses) (Rance & Starr, 2015). Elective inner hair cell loss being a cause of ANSD has been reported in a study by Amatuzzi et al. (2001) in premature infants. Other than this, in some animal studies, it has been found that prolonged hypoxia can cause a greater degree of damage to inner hair cells than to outer hair cells, but similar findings in adults have not been reported, where isolated loss is not usually present (Rance & Starr, 2015).

2.4.2 Inner Hair cell Ribbon Synapses

Defects in Ribbon synapses between inner hair cells and spiral ganglion have been found to cause genetic and acquired hearing loss. The function of these synapses is to allow for temporally precise, infatigable encoding of sound, and impairment in them can cause dysfunction of neural encoding and acoustic temporal cues that help in speech perception (Moser & Tobias, 2015). It has been reported by Moser et al., (2013) that a deficit in the release of neurotransmitter from ribbon synapses are a significant cause of deafness in neonates with abnormal ABR findings. These ABR findings are typically present along with normal summating potentials, and an abnormal compound action potential (Santarelli et al., 2015), indicating auditory neuropathy.

A mutation in the Otoferlin (encoded by OTOF) in humans, that is associated with temporary temperature dependent ANSD has been detected. It causes the individual to have normal hearing when afebrile, but have a severe impairment in hearing and a loss of both compound action potentials and affected ABR findings, when there is even a slight increase in body temperature (Starr et al., 1998; Varga et al., 2006).

2.4.3 Postsynaptic Mechanisms

Dendritic Nerve Terminals such as a pathology that affects the dendritic nerve terminals have results similar to those obtained with ribbon synapse disorders. Other than this, it has been found to reduce neural activity in the auditory nerve and brainstem, while sparing the cochlear hair cells, axonal neuropathies along with auditory nerve conduction disorders, hypoplasia of the auditory nerve, auditory ganglion cell disorders and Myelin disorders (Rance& Starr, 2015).

2.5 Auditory Profile of ANSD

Studies on individuals with ANSD report a wide variety in the degree of hearing losses that can vary from minimal to profound hearing loss (Davis & Hirsh, 1979; Rance & Starr, 2015). There also seems to be a variation in the audiometric configuration of these individuals, for instance in a study by Kumar and Jayaram (2006), out of 61 individuals that had a confirmed diagnosis of ANSD, 26 had a peaked audiogram, the slope/peak usually being at 2 kHz, 11 had flat, 11 rising, 8 saucer shaped, and 3 had bilaterally sloping configurations. Their degrees of hearing loss varied between mild and severe.

Berlin et.al., (2010) summarized the test findings and the management efforts of 260 individuals diagnosed with ANSD. They tried hearing aids in 85 of these patients, and cochlear implants on 49. Among these, around 15% reported some benefit from hearing aids for language learning, and 85% reported improvement in speech comprehension and language acquisition. Approximately 5% (13/260) of the total population developed normal speech and language without intervention. All participants had absent or abnormal auditory brainstem responses (ABR), often 'ringing' cochlear microphonics, and the presence or history of otoacoustic emissions. Etiologies and co-existing conditions included genetic, peripheral neuropathies, perinatal jaundice and/or anoxia and/or prematurity. Similar findings were reported in by Narne et.al., (2014), which is a retrospective study on 198 individuals diagnosed with ANSD, they found that most individuals had bilateral ANSD, with the male to female ratio being 1.25:1. Most had a rising audiometric pattern, with absent stapedial reflexes and ABR, and OAEs present. They stated that these individuals do benefit from hearing aids as evidenced by their LLR findings. They also add that the current predictors of recovery for these individuals are their speech identification scores and cortical auditory evoked potentials.

2.6 Acoustic Reflex

As mentioned earlier, individuals with ANSD usually have absent stapedial reflex. The middle ear stapedial reflex or acoustic reflex is mediated by the inner hair cell, eighth nerve and brainstem pathways. The absence of the acoustic reflex in the presence of OAEs therefore reflects some pathology at some point in this pathway it is a

striking feature in individuals with ANSD (Starr et al., 1996). It is the same case with both ipsilateral and contralateral reflexes in these individuals (Kumar & Jayaram, 2006).

In a study by Berlin et al., (2005) they evaluated a total of 136 individuals with ANSD, all of whom had normal otoacoustic emissions and found that none of these showed normal acoustic reflexes, whether contralaterally or ipsilaterally tested. Three individuals however, showed reflexes at 95 dB HL, but not at frequencies of 1 or 2 kHz.

2.7 Speech Perception

Individuals with ANSD, speech perception abilities may show difficulties varying from minimal to severe, and are exaggerated in the presence of competing background noise (Rance et al., 2004). Another feature of ANSD is that there is a significant impairment of speech recognition scores, that is disproportionate to their audiometric thresholds (Starr et al., 1996). As reported by Kumar and Jayaram (2006) where they evaluated the speech perception abilities of 61 individuals with ANSD, their results varied from no measurable speech identification score to 90% identification score, with 60% having no measurable scores. They found that there was a negative correlation between the scores obtained and the audiometric thresholds of these patients except at all octave frequencies tested (250 Hz to 8000 Hz) except at 8000 Hz, which they attributed to those subjects with no measurable speech perception abilities with mild to moderate hearing loss. They also compared the speech perception scores with the audiometric configuration and found that those individuals with peaked audiograms showed higher identification scores in both ears compared to those with other audiometric

configurations. However, they state that generalizations should not be made based on this data as the number of subjects with rising and saucer shaped audiograms were far too small.

Similar findings were reported in a recent study by Narne et., al (2014) where speech recognition scores for bisyllabic words in quiet were available in only 102 patients out of 173, and only in 33 when done in noise. The mean scores reported were 61% in the right ear and 62% in the left for children between 5 to 10 ten years of age, and only 44% of the 102 had speech recognition scores greater than 50%, while rest were below this. These difficulties may be a result of asynchronous firing of auditory nerve resulting in abnormal temporal coding (Rance et al., 2004). Speech perception in noise was also found to be difficult in children with ANSD than those with normal hearing, but it was not consistent across subjects and some of the children shows reasonable perceptual abilities at low signal to noise ratios (Rance et al., 2007).

2.8 Psychoacoustic Tests

Psychoacoustic experiments conducted on listeners with ANSD indicate a significant impairment in temporal processing that leads to extreme difficulty in understanding speech (Rance et al., 2004). Extensive psychoacoustic testing was conducted on two individuals with ANSD by Starr et al., (1996) and these tests revealed severely abnormal discrimination for frequency, intensity and duration, abnormal gap detection tests and a great difficulty in localizing sound based on both time and intensity cues.

Evaluation of temporal envelope processing ability using temporal modulation transfer function (TMTF) in individuals with ANSD have been studied, and results of these studies have shown that there is impaired ability in those with ANSD for detecting both slow and fast temporal modulations, with more impairment in processing faster modulations than slower modulations (Rance et al., 2004; Zeng, 2005). In a similar study by Narne (2013), temporal resolution of listeners with normal hearing and those with ANSD were evaluated using temporal modulation transfer function and frequency modulation detection at modulation rates 2 and 10 Hz. This was followed by evaluation of speech perception in quiet and in noise at SNR ratios of 0, 5 and 10 dB respectively. Result showed that these with ANSD showed significantly poorer performance than normal hearing listeners in both conditions. Also, there was a significant correlation seen between measures of temporal resolution and speech perception in noise. The author attributed these findings to an impaired ability to efficiently process envelope and fine structure cues in speech in individuals with ANSD.

Zeng et al., (2005) assessed lateralization for pure tone using phase cues and in detecting binaural beats in listeners with AN. They found that those with ANSD had an impaired ability to use phase cues and also in detecting beats. These findings are consistent with impaired processing of temporal fine structure information.

2.9 Auditory Brainstem Response measurement

Starr et al., (1991) have reported that a dys-synchrony in neural firing by even a fraction of millisecond can result in abnormal ABR with diminished waves. They state

that physiologically, there is a dysfunction of the auditory nerve in individuals with ANSD, and so we obtain absent or abnormal responses. This is possibly due to a decreased number of neural components required for the elicitation of a response.

Another feature of ANSD is an apparent lack of correlation between the measured air conduction thresholds and ABR, with even those having moderate hearing loss having absent ABRs. The measure of the time interval between the waves I and III has been used as an index of the conduction time between the distal portion of the VIII nerve within the cochlea and the central portion of the VIII nerve within the cochlear nucleus. The absence or abnormality of all neural components of the ABR is an indicator that the distal portions of the auditory nerve may be affected (Starr et al., 1996).In another study, ABR responses were found to be absent in 364 ears out of 392 tested and were present only on 28 ears with poor morphology. These findings were attributed to abnormal ABR findings because of temporal asynchrony (Narne, et al., 2014).

2.10 Late Latency Responses

Narne et al., (2014) report in their study that out of the 114 individuals tested, around 65% of the ears had cortical potentials present, in spite of having abnormal or absent ABRs. Of these, 28 ears out of 77 (36%) had a prolonged N1 latency with a mean latency of 187 ms (SD, 32.8), and 39 ears (64%) had latencies within normal limits with a mean latency of 102 ms (SD, 26.3). They found that individual can have good speech perception in quiet even though the brainstem responses were abnormal. Similar results

were previously reported by others, highlighting the importance of LLR testing (Starr et al., 1996).

Another conclusion that can be drawn from these findings is that good synchronization may not be a prerequisite for speech perception in quiet conditions, and that LLR can be used as an indicator of speech perception abilities of individuals with ANSD (Kraus et al., 2000).

2.11 Vestibular Evoked Myogenic Potentials

As the vestibular and cochlear branches are parts of the same fiber bundle system called the vestibulocochlear nerve, it is likely that neuropathy in one (cochlear branch) may also form a feature in the other (vestibular branch) (Kumar et al., 2007). In a study comparing a group 30 individuals without ANSD to 8 individuals with ANSD, the main measures compared were the that the mean peak latency (in ms) of the two early waves p13 and n23 of VEMP, and 8 of the test group normal response was detected in 3 ears (1 in right and 2 in left ears). There were unrepeatable waves in four ears and absent VEMPs in nine ears. However the sample size is too small to generalize results (Sazgar et al., 2010).

A study on 26 individuals with ANSD that underwent cVEMP and caloric testing revealed that there was an absence of responses in cVEMP and bilateral hypo-functional response in caloric tests in most individuals, indicating that there may be involvement of both superior and inferior portion of the vestibular nerve in individuals with ANSD (Sinha et al., 2014). A study by Singh, Sinha and Barman (2016) investigated the otolith

modulated function of those diagnosed with ANSD and found that both cVEMP and oVEMP were administered at 500 Hz tonebursts, where less than 20% responses were present for both potentials. Significant prolonged inter-peak and later peaks latency and significant decreased amplitudes in ANSD individuals than the control groups. These abnormal or absent responses indicated a dysfunction of superior and inferior vestibular nerves.

2.12 Otoacoustic Emissions (OAE)

ANSD presents with some very conflicting findings, as stated by Berlin et al., (2003), at one extreme, those with ANSD show to be total deafness despite normal OAEs., while at the other extreme, there are nearly normal audiograms with no auditory complaints except in noise despite a totally absent ABR. As mentioned earlier, the presence of OAEs in the absence of Acoustic Reflex Threshold and abnormal/absent ABR is a strong indicator of ANSD. Otoacoustic emissions have been used as an objective measure of outer hair cell integrity in the cochlea, in patients who are unable to give behavioral responses (eg, infants) or to confirm behavioral audiometric findings. The value of the combination of OAEs and measures of neural function at the level of the eighth cranial nerve and the brainstem has been demonstrated in patients undergoing clinical assessment for ANSD. Before the recognition of OAEs, presumptive hair cell function was assessed by recording CMs generated in response to acoustic signals. The presence of normal OAEs means that the outer hair cells in the cochleae are presumed to be normal. The status of the inner hair cells alone cannot be assessed with any currently available procedure (Madden, Rutter, Hilbert, Greinwald, & Choo, 2002).

OAEs are one of the most important diagnostic indicators for ANSD (Berlin et al., 2010) Previously, Hood and Berlin (2001) have noted that the amplitude of TEOAEs in individuals with ANSD is abnormally higher compared to individuals with normal hearing. The high amplitude has been attributed to lack of efferent suppression (Sininger & Starr, 2001).

In a study by Narne et al. (2014) where they evaluated OAEs and Cochlear microphonics for both ears in 198 individuals with ANSD, it was found that approximately three-quarters of the patients had present OAEs while the remaining one-quarter had either partial or absent responses. However, in a quarter of patients in whom OAEs were partial/absent, cochlear microphonics were present.

It was observed that the occurrence of SOAEs was higher at frequencies below 1.5 kHz in individuals with ANSD compared to individuals with normal hearing. It was also observed that greater numbers of individuals with ANSD had SOAEs present at multiple frequencies in comparison to those with normal hearing, when compared between a group of 30 normal hearing individuals and a same number of those with ANSD. The non- linear difference method with an unfiltered 80µs click was used to record SOAEs with the stimulus level auto-adjusted to 80 dB peSPL in the external ear canal. Time analysis was 20 ms and the power spectrum was generated by ILO V6 software (Mallat, 1989).Therefore individuals with ANSD may have some subtle auditory dysfunction at the level of the outer hair cells (OHCs) responsible for the cochlear active mechanism (Narne, Prabhu, & Chatni, 2014).

Another observation in individuals with ANSD is that there is disappearance of OAEs over a period of time. This, according to a study by Starr et al. (2000) could be attributed to middle ear disease or the use of amplification devices. In a study by Talaat et.al. (2013), that was done on 77 children diagnosed with ANSD, they found that there was a reduction in OAE amplitude with time, they speculate that this could be due to the spread of the pathological process to the Outer Hair cells after may initially predominantly affecting the Inner Hair Cells.

Narne, Prabhu and Chatni (2014) carried out time frequency analysis of Transient Evoked Otoacoustic Emissions (TEOAEs) in 22 individuals with ANSD. Findings between individuals with ANSD and a normal group were compared using wavelet transform method. Wavelet analysis divides the complex TEOAE waveforms into different frequency components at the generic time t and frequency f0 of the TEOAEs signal x (t) using the formula given by Mallat (1989). Confirmation of diagnosis was done previously using pure tone audiometry, ABR and Acoustic reflex measurement. Higher amplitude TEOAEs, with slightly shorter latencies for lower frequency signals than the normal control group were found in the clinical group, which were also thought to be caused by damage to the efferent system.

Data from a study by Campos and colleagues (2011) shows that contralateral acoustic stimulation significantly affects only the amplitude of the DPOAE I/O functions. The slope is affected as well, but not significantly so. This observation can tell us some information about the nature of CAS, suggesting that the latter is primarily a linear phenomenon without the cochlear compression and non-linear components seen in the

healthy cochlea. The DPOAE slope is the growth rate of the DPOAE response. They go on to explain that the slope value decreases at higher stimulus intensities, especially in the range from 50 to 80 dB peSPL, where the cochlear compression occurs. Cochlear compression decreases with the increased severity of cochlear lesions, so the DPOAE slope can represent a variable with high specificity and low sensitivity.

In terms of measuring input/output functions, Boege and Janssen (2002) derived DPOAE thresholds from DPOAE I/O functions that were extrapolated. They measured the Cubic 2f 1-2f 2 distortion products and pure tone threshold at f2 at 51 frequencies between f 2=500 Hz and 8 kHz at up to ten primary tone levels between L2=65 and 20 dB SPL in 30 normally hearing and 119 sensorineural hearing loss ears. They used an optimized primary tone level setting (L1 = 0.4L2 + 39 dB) that accounted for the nonlinear interaction of the two primaries at the DPOAE generation site at f2 , the pressure of the 2 f 1-f 2 distortion product is a linear function of the primary tone level L2. Linear regression yields correlation coefficients higher than 0.8 in the majority of the DPOAE I/O-functions. They stated that linear behavior was sufficiently fulfilled for all frequencies in normal and impaired hearing. This suggests that the observed linear functional dependency is quite general. There also state that there is a significant correlation between DPOAE threshold and pure tone threshold ($r=0.65$, $p<0.001$). Thus, according to these authors DPOAEs that reflect the functioning of an essential element of peripheral sound processing enable a reliable estimation of cochlear hearing threshold up to hearing losses of 50 dB HL without any statistical data.

It is known that Cochlear compression decreases with the increased severity of cochlear lesions, therefore the DPOAE slope can represent a variable with high specificity and low sensitivity. The DPOAE slope is the growth rate of the DPOAE response, and the slope value decreases at higher stimulus intensities, especially in the range from 50 to 80 dB peSPL, where the cochlear compression occurs Therefore, it is a valuable measure of cochlear functioning (Campos et al., 2011).

Similarly, since individual slopes alone may not give adequate information, the area function, or the sum of all the DP amplitudes above the noise floor, would provide a better estimate of the robustness of the DP I/O function (Gates et al., 2002)

Considering the findings hereto mentioned, and the methods available for the assessment of cochlear functioning, there seems to be a dearth of studies that evaluate the I/O functions in individuals with ANSD. Investigation on this front is warranted as there could be some subtle pathology at the cochlear level in these individuals, and it may help to better understand the pathopysiology of ANSD.

Chapter 3

METHODS

3.1 Participants

To fulfill the objective of the study, minimum of 30 ears (15 individuals) diagnosed as having auditory neuropathy spectrum disorder aged between 20 to 55 years, (mean age of 24 years, SD. 7.94) were included in the study. In addition, a comparison group of normal hearing young adults of the age range 18-25 (mean age of 21, SD. 2.07 years) was also considered.

3.2 Participant Selection criteria

3.2.1 Experimental Group

All the participants in the experimental group were selected based on the clinical diagnostic criteria suggested by Berlin et al. (2003) and Starr et al. (2000) as mentioned below:

- The cochlear amplification is preserved and this was decided based on presence of otoacoustic emissions
- The auditory nerve response is altered which was assessed based on the absent or severely abnormal auditory brainstem response
- None of them showed any evidence of space occupying lesion on routine neurological examination or through clinical neurological examination or CT/MRI which was done as and when required. In addition, the neurologist ruled

out other associated neuropathies and only individuals with diagnosis of primary auditory neuropathy by the neurologist were considered for the study.

- They had normal otologic findings on examination of ear canal by an experienced Otologist
- They showed immittance findings with A or As type tympanogram with absence of acoustic reflexes.

3.2.2 Control Group

- Individuals had pure tone average (PTA, average of pure tone thresholds at 500 Hz, 1 kHz, 2 kHz and 4 kHz) of less than 15 dB HL.
- None of the participants reported of having any middle ear disorder/pathology.
- All the participants had no history of otological complaints, noise exposure, ototoxic medications, diabetes/hypertension.

3.2.3 Test Environment

The testing was carried out in a sound treated room (two room set-up, for audiometry), with ambient noise levels under the levels prescribed by ANSI S3.1 1999.

3.3 Instrumentation

- Pure Tone Audiometry as done using a Calibrated GSI 61 audiometer, using TDH-39 headphones to obtain the air conduction thresholds and a B-71 Bone Vibrator for bone conduction thresholds.

- For immitance measurement, a calibrated GSI Tympstar Immitance meter was used, with a probe tone of 226 Hz to obtain the tympanogram. Acoustic reflex measurement was also done on the same instrument for both ipsilateral and contralateral reflex measurement at frequencies 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz.
- Auditory brainstem responses were obtained through a calibrated IHS or Biologic EP, through ER-3A insert receiver.
- A calibrated Otodynamics ILO V6 Echoport system was used to obtain the OAE I/O function.

3.4 Procedure

Pure tone behavioral thresholds were obtained using modified version of Hughson-Westlake procedure (Carhart & Jerger, 1959), where the intensity was reduced by 10 dB whenever the subject stated they heard the sound and an increase in 5 dB when they stopped hearing the sound. This was repeated till a threshold (intensity at which the subject heard the sound two out of three times) was obtained. This method was used to evaluate both the air and bone conduction thresholds.

Speech audiometry was done using spondees (to find speech recognition threshold), and phonemically balanced words (to find speech discrimination score).Middle ear function analysis was done using a calibrated tympanometer (GSI Tympstar V 2.0), with a probe tone of 226 Hz. Reflexes were measured both ipsilaterally and contralaterally at frequencies of 500 Hz, 1000 Hz, 2000 Hz and 4000Hz. This was followed by Auditory Brainstem Evaluation done using Intelligent Hearing System (IHS)

or Biologic EP. The stimulus was presented through an ER-3A insert receiver using standard test protocol.

3.4.1 Obtaining the DP I/O function

Measurements were done through a calibrated Otodynamics ILO V6 Echoport system. Distortion Product Otoacoustic Emissions were obtained for two tones, F1 and F2 (primaries), their ratio being 1.22, with intensities of 65 dB SPL and 55 dB SPL (L1 and L2) respectively. A probe tip of suitable size was selected for the participants who were made to sit comfortably on the chair.

The input-output function was then obtained for tones of frequencies 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz and 6 kHz, holding the frequency ratio between the test tones constant at 1.22, for different intensities. An average of three responses was taken for each individual response. The intensities were set according to the stimulus paradigm found to be optimal for clinical testing (Kummer, Janssen, Hulin, & Arnold, 2000; (Janssen, Niedermeyer, & Arnold, 2006) where primary tone stimulus is L1=(0.4*L2) +39dB SPL, as the L2 decreases in 5 dB steps. This accounts accounting for nonlinear interactions of the primaries at the generation site of the DPOAE at F2.

3.5 Analyses

The comparison of the DPOAE Input-Output function was done using two variables, the first being slope of the I/O function and the second being the area under the curve. These variables were compared between the normal group and the ANSD group, across different frequencies.

The slope was calculated using the linear trend model. The DPOAE I/O data were fitted with linear functions for the stimulus range from 65 to 35 dB SPL. Once a linear fit was obtained, the slope was estimated at 2 points of the x coordinate equal with x2=65 dB SPL and x1=35 dB SPL. Given the corresponding points of the DPOAE amplitude as y2 and y1, the slope of the fitted linear function was defined as: $b=(y2–y1)/(x2–x1)$.

The area under the curve was to be determined as the difference between the noise floor and the DP amplitude at all the 5 dB stimulus level steps from 65 dB SPL to 35 dB SPL. If the responses were below the noise floor, they were excluded from further analysis. The cumulative amplitude of the DP responses above the noise floor were multiplied by 5 and reported in $dBSPL^2$ ($area^2$). The square root of $area^2$ (i.e. area) was used for the analyses. This procedure for calculating the area was proposed by Gates and Rubel (2002).

3.6 Statistical Analyses

A Shapiro-Wilk's test for normality was done, and the data was not normally distributed ($p<0.05$), hence non-parametric tests were chosen for further analysis. Descriptive statistics for determining Mean, Standard Deviation, Minimum and Maximum were done for both Area and Slope measurements, for each test of the six test frequencies. A Mann-Whitney U test was done to compare the slope and area between the two groups, followed by within group comparisons of the ANSD group using the Friedman test and Wilcoxon signed rank test. Spearman's rank correlation was done to

determine the relationship between area and slope with pure tone average and speech identification.

3.7 Ethical Approval

Approval was taken from ethical approval committee of the institute and the testing was done using non-invasive procedures. The objectives and procedures of the study were explained to the participants before evaluation and informed consent was taken from them.

Chapter 4

RESULTS AND DISCUSSION

The study compared two groups, a control group of normal hearing individuals and an experimental group with ANSD. Each group had 15 participants (30 ears) each. Slopes and Area of DPOAE I/O function for six frequencies were compared between the two groups, and areas were even compared between frequencies for the ANSD group. All the data obtained was analyzed using statistical package of social science (SPSS) software version 20.0. The Shapiro Wilk's test of normality was administered to check whether the raw data is normally distributed or not and was found to be not normally distributed ($p<0.05$). Hence, the non-parametric tests were chosen.

The results of the study are explained under following headings:

4.1 Comparison of Slope and Area for each frequency between the control and experimental groups.

4.2 Comparison of slope and area separately between frequencies within the experimental group.

4.3 Correlation of Pure Tone Average with Slope and Area between the control and experimental groups.

4.4 Correlation of Speech identification Score with Slope and Area between the control and experimental groups.

4.1 Comparison of Slope and Area for each frequency between the control and experimental groups

Table 4.1 gives the Mean and Standard Deviation (SD), and the minimum and maximum slopes for each of the six test frequencies for both the control and experimental groups. The data showed that the normal group has higher mean scores than the ANSD group. The minimum values for the ANSD group are lower than the control for all frequencies except at 4 KHz, whereas maximum values for the lower frequencies (1 kHz, 1.5 kHz, 2 kHz) are higher in the ANSD group.

Table 4.1
Mean, Standard deviation (SD), Minimum, Maximum, and Median of the slopes of DPOAE I/O function in individuals with and without ANSD

	NORMAL				
	MEAN	**SD**	**MINIMUM**	**MAXIMUM**	**MEDIAN**
1 kHz	.53	.31	-.03	.94	.49
1.5 kHz	.66	.29	.00	.96	.73
2 kHz	.74	.24	.05	.95	.85
3 kHz	.81	.20	.11	1.0	.87
4 kHz	.84	.19	.13	.99	.91
6 kHz	.89	.18	.22	1.0	.96
	ANSD				
1 kHz	.45	.49	-.96	.98	.68
1.5 kHz	.60	.44	-.58	.99	.83
2 kHz	.58	.50	-.97	.98	.77
3 kHz	.72	.31	-.30	.99	.84
4 kHz	.80	.26	-.05	.99	.87
6 kHz	.80	.28	-.30	.99	.91

The Mean and Standard Deviation (SD), and the minimum and maximum area for each of the six test frequencies for both the control and experimental groups are described in Table 4.2. The mean score for the first three frequencies (1 kHz, 1.5 kHz, 2 kHz) are higher in the normal group whereas the last three frequencies (3 kHz, 4 kHz, 6 kHz) show the opposite finding with the ANSD group having higher mean scores.

Table 4.2
Mean, Standard deviation (SD), Minimum, Maximum, and Median of the areas of DPOAE I/O function in individuals with and without ANSD

	NORMAL				
	MEAN	**SD**	**MINIMUM**	**MAXIMUM**	**MEDIAN**
1 kHz	20.34	6.38	.93	30.91	16.99
1.5 kHz	24.30	5.20	13.06	31.58	24.07
2 kHz	23.42	4.64	13.08	29.39	24.89
3 kHz	20.96	3.73	10.89	27.84	20.61
4 kHz	22.73	3.85	10.51	28.89	22.29
6 kHz	23.42	4.38	11.75	29.74	22.97
	ANSD				
1 kHz	17.33	4.99	4.74	25.90	18.35
1.5 kHz	21.52	5.05	11.73	29.15	22.62
2 kHz	21.09	4.54	13.06	28.50	21.82
3 kHz	21.84	3.86	10.12	27.22	22.17
4 kHz	23.58	3.79	12.29	29.09	24.51
6 kHz	23.87	5.2	12.62	30.70	26.31

The values for slope (figure 4.1) and areas (figure 4.2) for individuals with and without ANSD were compared between the two groups using the Mann-Whitney U test. Significant differences ($p<0.05$) were noticed between the two groups for both slope and area at the low frequencies 1 kHz, 1.5 kHz and 2 kHz. There was no significant difference ($p>0.05$) between the two groups for both slope and area at 3 kHz, 4 kHz and 6 kHz.

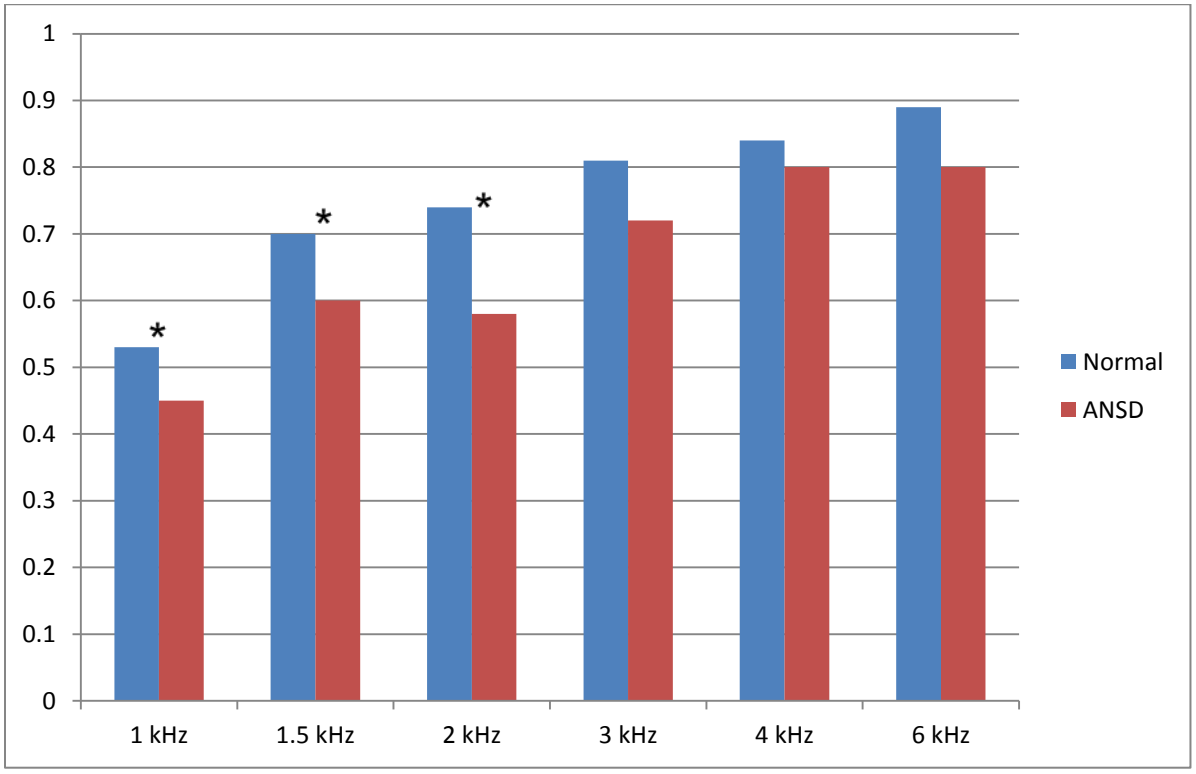

Figure 4.1 Comparison of mean Slope between individuals with and without ANSD.

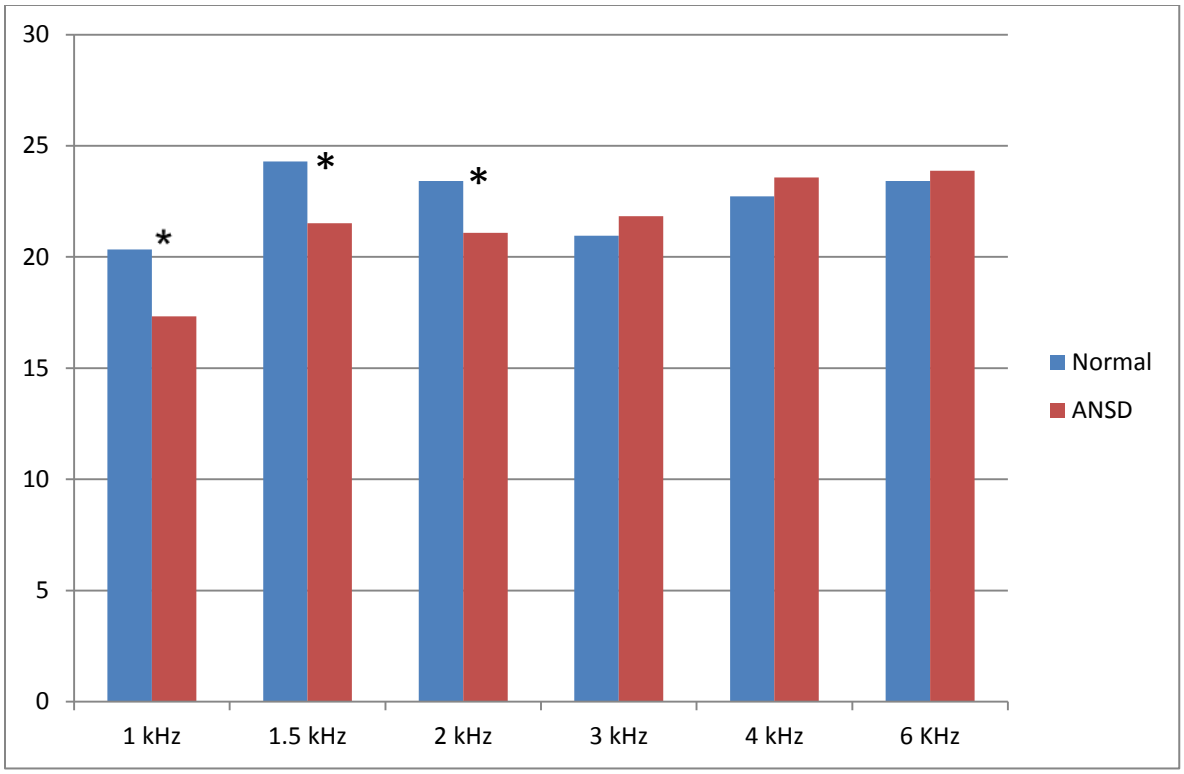

Figure 4.2 Comparison of mean Area between individuals with and without ANSD (*p<0.05).

4.2 Comparison of Area and slope between frequencies within the experimental group.

Friedman's tests were done to compare the area and slope across frequencies in the ANSD group. The results showed that there was a significant difference between the different frequencies ($p<0.05$) across frequencies for both slope and area. The results of Friedman's test are shown in Table 4.3. Wilcoxon signed rank tests were done to compare the DPOAE I/O slope and areas of each frequency with the others in the ANSD group. There was a significant difference ($p<0.05$) found when the lower frequencies (1 kHz, 1.5 kHz and 2 kHz) were compared with high frequency (3 kHz, 4 kHz, 6 kHz). But

there was no significant difference ($p>0.05$) found among the low frequencies and high frequencies when they were compared within their respective groups.

Table 4.3

Test Statistics for Friedman's test for slope and area of DPOAE I/O function for individuals with ANSD

	Slope	**Area**
Chi-Square	18.21	42.99
Degree of Freedom	5	5
Significance	.003	.000

4.3 Correlation of Pure Tone Average with Slope and Area for individuals with ANSD

A Spearman's correlation test was done to check for any correlation between DPOAE I/O Slope and Area with the pure tone average of the participants with ANSD. The Spearman's Rho values are described in Table 4.4. There were no significant correlations observed.

Table 4.4

*Spearman's coefficient values for Individuals with ANSD, comparing Hearing loss with Slope and Area of I/O curve (*correlation significant at the 0.05 level, **correlation significant at the 0.01 level)*

Frequency		**1KHz**	**1.5 KHz**	**2 KHz**	**3 KHz**	**4 KHz**	**6 KHz**
Slope	Rho	.028	.000	-.222	.401	.167	.168
	Sig	.883	.999	.239	.028	.378	.375
Area	Rho	.207	.172	-.189	.074	.145	-.035
	Sig	.272	.364	.316	.696	.446	.853

4.4 Correlation of Speech identification Scores with Slope and Area for individuals with ANSD

Similarly, a Spearman's correlation test was done to check for any correlation between DPOAE I/O Slope and Area with the speech intelligibility scores of the participants with ANSD. The Spearman's Rho values are described for the experimental group in Table 4.5. Significant correlations were observed for slope at frequencies 2 kHz and 3 kHz. However, the correlations obtained were weak.

Table 4.5

*Spearman's coefficient values for Individuals with ANSD, comparing speech identification scores with Slope and Area of I/O curve (*correlation significant at the 0.05 level **correlation significant at the 0.01 level)*

Frequency		**1KHz**	**1.5 KHz**	**2 KHz**	**3 KHz**	**4 KHz**	**6 KHz**
Slope	Rho	-.083	.026	.418*	-.499**	-.160	-.283
	Sig.	.664	.892	.022	.005	.399	.129
Area	Rho	-.014	-.024	.154	-.184	-.233	-.157
	Sig.	.943	.900	.417	.331	.251	.407

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This study was done to compare the DPOAE I/O slope and Area across six frequencies, between an experimental group of individuals with ANSD and a control group of individuals who do not. These tests were chosen in light of previous studies, that report a difference in the properties of OAE are different in individuals with ANSD compared to normal control. As reported in the study by Kumar, Avilala, Mohan and Barman (2012), where it was found that SOAEs show a different spectral distribution (<1.5 kHz) in the ANSD group versus the normal control group (>1.5 kHz), along with greater numbers of multiple SOAEs. These changes were attributed to subtle impairment in the functioning of the cochlea and the medial olivocochlear system. Similar attributions were made by Narne, Prabhu and Chatni (2014) to account for the higher amplitude and slightly shorter latencies of TEOAEs for lower frequency signals than the normal control group were found in the clinical group.

In our study, it was found that maximum values of slope were greater for the lower frequencies (1 kHz, 1.5 kHz, 2 kHz) in the ANSD group. However, the overall means were lower than those of the control. This trend was reported in the previous studies as well, with the lower frequency regions showing some difference from the control group. There was significant difference found in the first 3 frequencies, where their mean slopes were lesser than the control group. Similarly for the area, the difference was observed in the first three frequencies with the control group having greater area and the experimental group had greater differences in the last three frequencies. This indicates that the lower frequency OAE responses are affected in ANSD, and that these regions function differently from the control group. Since the input-output function slope obtained for different input levels, is directly reliant on cochlear health (Rasetshwane et al., 2015) and therefore this difference could indicate a subtle dysfunction at the level of the cochlea. This shows that there are some differences in the cochlear functioning of individuals with ANSD, despite previous assumptions that they have normal cochlear functioning.

Correlation between the Hearing loss and Speech Identification Score the I/O slope and area was revealed to be weak. This is expected since hearing loss in ANSD is mostly likely cause by greater damage to inner hair cells, and the reduction in speech identification scores a reflection of dysfunction in the transmission of temporal characteristics through the Auditory nerve. Neither is caused by outer hair cell dysfunction and therefore they cannot predict the I/O slope or area, which on the other hand is entirely dependent on it.

Chapter 5

SUMMARY AND CONCLUSIONS

Auditory Neuropathy Spectrum Disorder (ANSD) is an electrophysiological diagnosis that is reached when test results indicate the presence of Evoked Otoacoustic Emission (OAEs), cochlear microphonics, absent or abnormal Evoked Auditory Brainstem Responses, absent Stapedial reflex and variable behavioral hearing thresholds. Even though a lot of research has been dedicated to finding the specific etiology of ANSD, the results remain more or less inconclusive (Starr, Picton, Sininger, Hood, & Berlin, 1996). Mostly, ANSD is attributed to dysfunction at the inner hair cells, the junction of the spiral ganglion cells and/or the auditory nerve (M. Amatuzzi et al., 2011; Nachman, 2012; Rohr, 2011).But, since OAEs are usually present and robust in these individuals despite the variation in etiologies, Otoacoustic emissions (OAEs) are routinely used clinically to assess cases of ANSD, having proven to be a valuable diagnostic tool (C. I. Berlin et al., 2010).

OAEs are pre-neural phenomenon that occurs at the level of the cochlea. Distortion Product OAEs (DPOAEs) are produced when two tones interact on the basilar membrane. OAEs are one of the most important diagnostic indicators for ANSD (Berlin et al., 2010). Hood and Berlin (2001) have noted that the amplitude of TEOAEs in individuals with ANSD is abnormally higher compared to individuals with normal hearing. The high amplitude has been attributed to lack of efferent suppression (Sininger& Starr, 2001).

It is known that Cochlear compression decreases with the increased severity of cochlear lesions; therefore the DPOAE slope can represent a variable with high specificity and low sensitivity. The DPOAE slope is the growth rate of the DPOAE response, and the slope value decreases at higher stimulus intensities, especially in the range from 50 to 80 dB peSPL, where the cochlear compression occurs. Therefore, it is a valuable measure of cochlear functioning (Campos et al., 2011). The input-output function slope obtained for different input levels, is directly reliant on cochlear health and therefore gives a picture of the supra-threshold nonlinear characteristics of the cochlea. Similarly, since individual slopes alone may not give adequate information, the area function, or the sum of all the DP amplitudes above the noise floor, would provide a better estimate of the robustness of the DP I/O function. This study was done in order to evaluate cochlear functioning in individuals with ANSD, using the measures of slope and area of DPOAE I/O function, in order to shed more light on the pathophysiology of this condition.

Traditionally, cochlear functioning is reported to be normal in individuals with ANSD. However, there are studies which report that the properties of OAE are different in individuals with ANSD compared to normal control (Kumar, Avilala, Mohan & Barman, 2012; Narne, Prabhu & Chatni, 2014). There are no studies which have attempted to explore the differences in cochlear non-linearity, if any in individuals with ANSD. It is well reported that DPOAE input-output function can explore the changes in cochlear functioning. Thus, the present study attempts to investigate the differences DPOAE input-output function (in terms of slope and area) between individuals with

normal hearing and ANSD. It is also attempted to study these differences, if any across different frequencies. In addition, it is also attempted to correlate the results of DPOAE input-output function with pure tone average and speech identification scores in individuals with ANSD. Hence, the study would help in exploring and understanding the patho-physiology of ANSD. The aim of the study is to evaluate distortion product otoacoustic emissions input-output function in individuals with auditory neuropathy spectrum disorder.

An experimental group consisting of participants selected on the basis of the clinical diagnostic criteria suggested by Berlin et al.(2003) and Starr et al.(2000), were compared with a control group of normal hearing individuals who had pure tone average (PTA, average of pure tone thresholds at 500 Hz, 1 kHz, 2 kHz and 4 kHz) of less than 15 dB HL. None of the participants reported of having any middle ear disorder/pathology. All the participants had no history of otological complaints, noise exposure, ototoxic medications, diabetes/hypertension. All testing was carried out in a sound treated room (two room set-up, for audiometry), with ambient noise levels under the levels prescribed by ANSI S3.1 1999.

Pure tone behavioral thresholds were obtained using modified version of Hughson-Westlake procedure (Carhart & Jerger, 1959), where the intensity was reduced by 10 dB whenever the subject stated they heard the sound and an increase in 5 dB when they stopped hearing the sound. This was repeated till a threshold (intensity at which the subject heard the sound two out of three times). This method was used to evaluate both the air and bone conduction thresholds.

Speech audiometry was done using spondees (to find speech recognition threshold), and phonetically balanced words (to find speech discrimination score).Middle ear function analysis was done using a calibrated tympanometer (GSI Tympstar V 2.0), with a probe tone of 226 Hz. Reflexes were measured both ipsilateraly and contralaterally at frequencies of 500 Hz, 1000 Hz, 2000 Hz and 4000Hz. This was followed by Auditory Brainstem Evaluation done using Intelligent Hearing System (IHS) or Biologic EP. The stimulus was presented through an ER-3A insert receiver using standard test protocol.

The input-output function was then obtained for tones of frequencies 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz and 6 kHz, holding the frequency ratio between the test tones constant at 1.22, for different intensities. The slope was calculated using the linear trend model. The DPOAE I/O data were fitted with linear functions for the stimulus range from 65 to 35 dB SPL. Once a linear fit was obtained, the slope was estimated at 2 points of the x coordinate equal with x2=65 dB SPL and x1=35 dB SPL. Given the corresponding points of the DPOAE amplitude as y2 and y1, the slope of the fitted linear function was defined as: $b = (y2–y1)/(x2–x1)$.

The area under the curve was to be determined as the difference between the noise floor and the DP amplitude at all the 5 dB stimulus level steps from 65 dB SPL to 35 dB SPL. If the responses were below the noise floor, they were excluded from further analysis. The cumulative amplitude of the DP responses above the noise floor were multiplied by 5 and reported in $dBSPL^2$ ($area^2$). The square root of $area^2$ (i.e. area) was used for the analyses. This procedure for calculating the area was proposed by Gates and Rubel (2002).

A Shapiro-Wilk's test for normality was done, and the data was not normally distributed ($p<0.05$), hence non-parametric tests were chosen for further analysis. Descriptive statistics for determining Mean, Standard Deviation, Minimum and Maximum were done for both Area and Slope measurements, for each test of the six test frequencies. A Mann-Whitney U test was done to compare the slope and area between the two groups, followed by within group comparisons of the ANSD group using the Friedman's test and Wilcoxon signed rank test.

The results showed that, there was a significant difference between both the DPOAE I/O slope and area at lower frequencies (1 kHz, 1.5 kHz and 2 kHz). Both the slope and area were found to be lesser in the ANSD group when compared to the control for these frequencies. This suggests that there is a difference in the OAE functioning in individuals with ANSD at the lower frequencies. Therefore the assumption of normal cochlear functioning in individuals with ANSD may not be true, and some subtle pathology may be present.

In terms of establishing a correlation between DPOAE I/O slope and area with Hearing Loss and Speech Identification score, it was found that there was no relation present. This can be because the OAEs are generated in the OHCs while the hearing loss which can be attributed to inner hair cell dysfunction and poor speech identification scores are probably being due to dysfunction in the firing rate of the auditory nerve.

5.1 Advantages of the study

- There have been no studies comparing the nonlinearity of cochlear functioning between individuals with ANSD and individuals without ANSD.

- Provides more insight into the pathophysiology of ANSD.

5.2 Limitations of the Study

- The study could have been done on a larger sample, as there is great heterogeneity in individuals with ANSD with respect to hearing thresholds, speech identification score and OAE.

5.3 Future Directions

- The study can be done on larger population.
- Effect of Contralateral suppression on DPOAE I/O slope and area for individuals with ANSD can also be studied.

References

Amatuzzi, M. G., Northrop, C., Liberman, M. C., Thornton, A., Halpin, C., Herrmann, B., … Eavey, R. D. (2001). Selective Inner Hair Cell Loss in Premature Infants and Cochlea Pathological Patterns From Neonatal Intensive Care Unit Autopsies. *Archives of Otolaryngology–Head & Neck Surgery*, *127*(6), 629. http://doi.org/10.1001/archotol.127.6.629

Amatuzzi, M., Liberman, M. C., & Northrop, C. (2011). Selective Inner Hair Cell Loss in Prematurity: A Temporal Bone Study of Infants from a Neonatal Intensive Care Unit. *Journal of the Association for Research in Otolaryngology*, *12*(5), 595–604. http://doi.org/10.1007/s10162-011-0273-4

Berlin, C. (1999). Auditory Neuropathy: Using OAEs and ABRs from Screening to Management. *Seminars in Hearing*, *20*(4), 307–314. http://doi.org/10.1055/s-0028-1082946

Berlin, C. I., Hood, L. J., Morlet, T., Wilensky, D., John, P. St., Montgomery, E., & Thibodaux, M. (2005). Absent or Elevated Middle Ear Muscle Reflexes in the Presence of Normal Otoacoustic Emissions: A Universal Finding in 136 Cases of Auditory Neuropathy/Dys-synchrony. *Journal of the American Academy of Audiology*, *16*(8), 546–553. http://doi.org/10.3766/jaaa.16.8.3

Berlin, C. I., Hood, L. J., Morlet, T., Wilensky, D., Li, L., Mattingly, K. R., … Frisch, /. (2010). Multi-site diagnosis and management of 260 patients with auditory

neuropathy/dys-synchrony (auditory neuropathy spectrum disorder). *International Journal of Audiology*, *49*(1), 30–43. http://doi.org/10.3109/14992020903160892

Berlin, C. I., Li, L., Hood, L. J., Morlet, T., Rose, K., & Brashears, S. (2002). Auditory neuropathy/dys-synchrony: After the diagnosis, then what? *Seminars in Hearing*, *23*(3), 209–214. http://doi.org/10.1055/s-2002-34458

Berlin, Hood, L. J., Morlet, T., Rose, K., & Brashears, S. (2003). Auditory Neuropathy/Dys-Synchrony: Diagnosis and Management. *Mental Retardation and Developmental Disabilities Research Reviews*. http://doi.org/10.1002/mrdd.10084

Bhat, J. S., Kumar, K., & Sinha, S. K. (2007). Auditory Neuropathy/Dys-synchrony In School-aged Hearing-impaired Children: A South Indian Perspective. *Asia Pacific Journal of Speech, Language and Hearing*, *10*(3), 157–164. http://doi.org/10.1179/136132807805297512

Bielecki, I., Horbulewicz, A., & Wolan, T. (2012). Prevalence and risk factors for Auditory Neuropathy Spectrum Disorder in a screened newborn population at risk for hearing loss. *International Journal of Pediatric Otorhinolaryngology*, *76*(11), 1668–1670. http://doi.org/10.1016/J.IJPORL.2012.08.001

Boege, P., Janssen, T., Boege, P., & Janssen, T. (2002). Pure-tone threshold estimation from extrapolated distortion product otoacoustic emission I / O-functions in normal and cochlear hearing loss ears Pure-tone threshold estimation from extrapolated distortion product otoacoustic emission I Õ O-functions in n, *1810*.

http://doi.org/10.1121/1.1460923

Campos, U. D. P., Hatzopoulos, S., Kochanek, K., Sliwa, L., Skarzynski, H., & Carvallo, R. M. M. (2011). Contralateral suppression of otoacoustic emissions: input-output functions in neonates. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*, *17*(10), CR557-62. http://doi.org/881981 [pii]

Campos, U. de P., & Carvallo, R. M. M. (2011). Correlation between DPOAE I/O functions and pure-tone thresholds. *Brazilian Journal of Otorhinolaryngology*, *77*(6), 754–760.

Carhart, R., & Jerger, J. (1959). Preferred method for clinical determination of pure-tone thresholds. *Journal of Speech & Hearing Disorders*. Retrieved from http://doi.apa.org/?uid=1960-07052-001

Davis, H., & Hirsh, S. K. (1979). A Slow Brain Stem Response for Low-Frequency Audiometry. *International Journal of Audiology*, *18*(6), 445–461. http://doi.org/10.3109/00206097909072636

Draper, T. H. J., & Bamiou, D.-E. (2009). Auditory neuropathy in a patient exposed to xylene: case report. *The Journal of Laryngology & Otology*, *123*(4), 462. http://doi.org/10.1017/S0022215108002399

Gates, G. A., Mills, D., Nam, B.-H., D 'agostino, R., & Rubel, E. W. (2002). Effects of age on the distortion product otoacoustic emission growth functions. *Hearing Research*, *153*, 53–60. Retrieved from

http://depts.washington.edu/rubelab/personnel/gates et al, HrRes.pdf

Janssen, T., Niedermeyer, H. P., & Arnold, W. (2006). Diagnostics of the Cochlear Amplifier by Means of Distortion Product Otoacoustic Emissions. *ORL*, *68*(6), 334–339. http://doi.org/10.1159/000095275

Kraus, N., Bradlow, A. R., Cheatham, M. A., Cunningham, J., King, C. D., Koch, D. B., … Wright, B. A. (2000). Consequences of neural asynchrony: A case of auditory neuropathy. *Journal of the Association for Research in Otolaryngology*, *1*(1), 33–45. http://doi.org/10.1007/s101620010004

Kumar, K., Kumar Sinha, S., Kumar Singh, N., Kumar Bharti, A., Barman, A., & Kumar, A. (2007). Asia Pacific Journal of Speech, Language and Hearing Vestibular Evoked Myogenic Potential as a Tool to Identify Vestibular Involvement in Auditory Neuropathy. *Asia Pacific Journal of Speech, Language and Hearing*, *10*(3), 181–187. http://doi.org/10.1179/136132807805297530doi.org/10.1179/136132807805297530

Kumar, U. A., & Jayaram, M. (2006). Prevalence and audiological characteristics in individuals with auditory neuropathy/auditory dys-synchrony. *International Journal of Audiology*, *45*(6), 360–6. http://doi.org/10.1080/14992020600624893

Kumar, U. A., & Jayaram, M. M. (2006). Prevalence and audiological characteristics in individuals with auditory neuropathy/auditory dys-synchrony. *International Journal of Audiology*, *45*(6), 360–366. http://doi.org/10.1080/14992020600624893

Kumar, V., Avilala, Y., Mohan, D., & Barman, A. (2012). Spontaneous otoacoustic emissions in individuals with auditory neuropathy spectrum disorder, (January), 50–54. http://doi.org/10.3109/1651386X.2012.657776

Kummer, P., Janssen, T., Hulin, P., & Arnold, W. (2000). Optimal L 1− L 2 primary tone level separation remains independent of test frequency in humans. *Hearing Research*, *146*(1–2), 47–56. http://doi.org/https://doi.org/10.1016/S0378-5955(00)00097-6

Lonsbury-Martin, B. L., & Martin, G. K. (1990). The clinical utility of distortion-product otoacoustic emissions. *Ear and Hearing*. http://doi.org/10.1097/00003446-199004000-00009

Madden, C., Rutter, M., Hilbert, L., Greinwald, Jr, J. H., & Choo, D. I. (2002). Clinical and Audiological Features in Auditory Neuropathy. *Archives of Otolaryngology–Head & Neck Surgery*, *128*(9), 1026. http://doi.org/10.1001/archotol.128.9.1026

Mallat, S. G. (1989). A theory for multiresolution signal decomposition: the wavelet representation. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, *11*(7), 674–693. http://doi.org/10.1109/34.192463

Manchaiah, V. K. C., Zhao, F., Danesh, A. A., & Duprey, R. (2011). The genetic basis of auditory neuropathy spectrum disorder (ANSD). *International Journal of Pediatric Otorhinolaryngology*, *75*, 151–158. http://doi.org/10.1016/j.ijporl.2010.11.023

Mittal, R., Ramesh, A. V., Panwar, S. S., Nilkanthan, A., Nair, S., & Mehra, P. R. (2012).

Auditory neuropathy spectrum disorder: Its prevalence and audiological characteristics in an Indian tertiary care hospital. *International Journal of Pediatric Otorhinolaryngology*, *76*(9), 1351–1354. http://doi.org/10.1016/j.ijporl.2012.06.005

Moser, T., Predoehl, F., & Starr, A. (2013). Review of Hair Cell Synapse Defects in Sensorineural Hearing Impairment. *Otology & Neurotology*, *34*(6), 995–1004. http://doi.org/10.1097/MAO.0b013e3182814d4a

Moser, & Tobias. (2015). Pathophysiology of Auditory Neuropathy and Synaptopathy. *Journal of International Advanced Otology*, *11*, 15–15. Retrieved from http://web.b.ebscohost.com/abstract?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=13087649&AN=103260531&h=RAU%2F%2B0iKsZcKgdWRG13cTCp6pgU3DPULlah%2BGuJhe8f0KDhBC%2F5%2BsLZ5f%2F6UYG7oXq%2BMqQxNQZaHWu19STBr2A%3D%3D&crl=c&resultNs=AdminWebAuth&r

Nachman, A. J. (2012). Retrocochlear hearing loss in infants: a case study of juvenile pilocytic astrocytoma. *International Journal of Audiology*, *51*(8), 640–644. http://doi.org/10.3109/14992027.2012.684404

Narne, V. K. (2013). Temporal Processing and Speech Perception in Noise by Listeners with Auditory Neuropathy. *PLoS ONE*, *8*(2), e55995. http://doi.org/10.1371/journal.pone.0055995

Narne, V. K., Prabhu, P., Chandan, H. S., & Deepthi, M. (2014). Audiological profiling of 198 individuals with auditory neuropathy spectrum disorder. *Hearing, Balance*

and Communication, *12*(3), 112–120. http://doi.org/10.3109/21695717.2014.938481

Narne, V. K., Prabhu, P. P., & Chatni, S. (2014). Time frequency analysis of transient evoked-otoacoustic emissions in individuals with auditory neuropathy spectrum disorder. *Hearing Research*, *313*, 1–8. http://doi.org/https://doi.org/10.1016/j.heares.2014.04.005

Prabhu, P., Kumar Yadav Avilala, V., & Manjula, P. (2012). Predisposing Factors in Individuals with Late- Onset Auditory Dys-Synchrony. *Asia Pacific Journal of Speech, Language and Hearing*, *15*(1), 41–50. http://doi.org/10.1179/136132812805253758

R. Hinchcliffe, B.O. Osuntokun, A. O. A. (1972). Hearing Levels in Nigerian Ataxic Neuropathy. *Audiology*, *11*, 218–230. Retrieved from http://www.isa-audiology.org/periodicals/1971-2001_Audiology/1972, Audiology, Vol. 11/No. 3-4 (161-264)/Hinchcliffe Osuntokun Adeuja, Audiology, 1972.pdf

Rance, G., & Barker, E. J. (2009). Speech and language outcomes in children with auditory neuropathy/dys-synchrony managed with either cochlear implants or hearing aids. *International Journal of Audiology*, *48*(6), 313–320. http://doi.org/10.1080/14992020802665959

Rance, G., Barker, E., Mok, M., Dowell, R., Rincon, A., & Garratt, R. (2007). Speech Perception in Noise for Children with Auditory Neuropathy/Dys-Synchrony Type Hearing Loss. *Ear and Hearing*, *28*(3), 351–360.

http://doi.org/10.1097/AUD.0b013e3180479404

Rance, G., Beer, D. E., Cone-Wesson, B., Shepherd, R. K., Dowell, R. C., King, A. M., … Clark, G. M. (1999). Clinical findings for a group of infants and young children with auditory neuropathy. *Ear and Hearing*, *20*(3), 238–52. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10386850

Rance, G., McKay, C., & Grayden, D. (2004). Perceptual Characterization of Children with Auditory Neuropathy. *Ear and Hearing*, *25*(1), 34–46. http://doi.org/10.1097/01.AUD.0000111259.59690.B8

Rance, G., & Starr, A. (2015). Pathophysiological mechanisms and functional hearing consequences of auditory neuropathy. *Brain*, *138*(11), 3141–3158. http://doi.org/10.1093/brain/awv270

Rasetshwane, D. M., Fultz, S. E., Kopun, J. G., Gorga, M. P., & Neely, S. T. (2015). Reliability and Clinical Test Performance of Cochlear Reflectance. *Ear and Hearing*, *36*(1), 111–124. http://doi.org/10.1097/AUD.0000000000000089

Rasetshwane, D. M., Neely, S. T., Kopun, J. G., & Gorga, M. P. (2013). Relation of distortion-product otoacoustic emission input-output functions to loudness. *The Journal of the Acoustical Society of America*, *134*(1), 369–83. http://doi.org/10.1121/1.4807560

Rea, P. A., & Gibson, W. P. R. (2003). Evidence for surviving outer hair cell function in congenitally deaf ears. *The Laryngoscope*, *113*(11), 2030–4. Retrieved from

http://www.ncbi.nlm.nih.gov/pubmed/14603069

Rohr, R. von. (2011). Cochlear Implant Impedance Telemetry Measurements and Model Calculations to Estimate Modiolar Currents. *Uzh.Ch*. Retrieved from http://www.uzh.ch/orl/publications/dissertations/master_thesis_rahel_von_rohr.pdf

Santarelli, R., Rossi, R., Scimemi, P., Cama, E., Valentino, M. L., La Morgia, C., … Carelli, V. (2015). OPA1-related auditory neuropathy: site of lesion and outcome of cochlear implantation. *Brain*, *138*(3), 563–576. http://doi.org/10.1093/brain/awu378

Sanyelbhaa Talaat, H., Khalil, L. H., Khafagy, A. H., Alkandari, M. M., & Zein, A. M. (2013). Persistence of otoacoustic emissions in children with auditory neuropathy spectrum disorders. *International Journal of Pediatric Otorhinolaryngology*, *77*(5), 703–706. http://doi.org/10.1016/J.IJPORL.2013.01.022

Sazgar, A. A., Yazdani, N., Rezazadeh, N., Yazdi, A. K., Alireza, &, & Yazdi, K. (2010). Acta Oto-Laryngologica Vestibular evoked myogenic potential (VEMP) in patients with auditory neuropathy: Auditory neuropathy or audiovestibular neuropathy? Vestibular evoked myogenic potential (VEMP) in patients with auditory neuropathy: Auditory neuropathy or audiovestibular neuropathy? *Acta Oto-Laryngologica*, *130*, 1130–1134. http://doi.org/10.3109/00016481003727582

Singh, N. K., Sinha, S. K., & Barman, A. (2016). Assessment of otolith mediated neural reflexes through cervical and ocular vestibular evoked myogenic potentials in individuals with auditory neuropathy spectrum disorders. *Hearing, Balance and*

Communication, *14*(2), 77–90. http://doi.org/10.3109/21695717.2016.1152047

Sininger, Y., & Starr, A. (2001). *Auditory neuropathy : a new perspective on hearing disorders*. Singular Thomson Learning. Retrieved from https://books.google.co.in/books?hl=en&lr=&id=HBqNRXtI2zAC&oi=fnd&pg=PA15&dq=onset+of+auditory+neuropathy&ots=javeDy-jb0&sig=wMp2T6WvrRQNarAQs-g5OpaCvLc#v=onepage&q=onset of auditory neuropathy&f=false

Starr, A. ., Sininger, Y. ., Winter, M. ., Derebery, M. J. ., Oba, S. ., & Michalewski, H. J. (1998). Transient Deafness Due To Temperature-Sensitive Auditory Neu... : Ear and Hearing. *Ear and Hearing*, *19*(3), 169–179. Retrieved from http://journals.lww.com/ear-hearing/Abstract/1998/06000/Transient_Deafness_Due_To_Temperature_Sensitive.1.aspx

Starr, A., McPherson, D., Patterson, J., Don, M., Luxford, W., Shannon, R., … Waring, M. (1991). Absence of Both Auditory Evoked Potentials and Auditory Percepts Dependent on Timing Cues. *Brain*, *114*(3), 1157–1180. http://doi.org/10.1093/brain/114.3.1157

Starr, A., Picton, T. W., Sininger, Y. Y., Hood, L. J., & Berlin, C. I. (1996). Auditory neuropathy. *Brain*, *119 (Pt 3*(3), 741–753. http://doi.org/10.1097/00020840-199810000-00008

Starr, A., Sininger, Y., & Pratt, H. (2000). The varieties of auditory neuropathy. *Journal of Basic and Clinical Physiology and Pharmacology*, *11*(3), 215–30.

Sujeet, K. S., Niraj, K. S., Animesh, B., Rajeshwari, G., & Sharanya, R. (2014). Cervical vestibular evoked myogenic potentials and caloric test results in individuals with auditory neuropathy spectrum disorders. *Journal of Vestibular Research*, *24*(4), 313–323. http://doi.org/10.3233/VES-140510

Teagle, H. F. B., Roush, P. A., Woodard, J. S., Hatch, D. R., Zdanski, C. J., Buss, E., … King, J. (2013). Benefits and Risks of Cochlear Implants. *Current Opinion in Otolaryngology & Head and Neck Surgery*, *6*(May), 356–362. http://doi.org/10.1080/00016480260000012

Varga, R., Avenarius, M. R., Kelley, P. M., Keats, B. J., Berlin, C. I., Hood, L. J., … Kimberling, W. J. (2006). OTOF mutations revealed by genetic analysis of hearing loss families including a potential temperature sensitive auditory neuropathy allele. *Journal of Medical Genetics*, *43*(7), 576–81. http://doi.org/10.1136/jmg.2005.038612

Vignesh, S. S., Jaya, V., & Muraleedharan, A. (2016). Prevalence and Audiological Characteristics of Auditory Neuropathy Spectrum Disorder in Pediatric Population: A Retrospective Study. *Indian Journal of Otolaryngology and Head & Neck Surgery*, *68*(2), 196–201. http://doi.org/10.1007/s12070-014-0759-6

Zeng, F.-G. (2005). Perceptual Consequences of Disrupted Auditory Nerve Activity.

Journal of Neurophysiology, *93*(6), 3050–3063. http://doi.org/10.1152/jn.00985.2004