Correlation between vHIT and caloric test in individuals with Auditory Neuropathy Spectrum Disorder

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CERTIFICATE

This is to certify that this dissertation entitled "**Correlation between vHIT and caloric test in individual with Auditory Neuropathy Spectrum Disorder**" bonafide work submitted in part fulfillment for the degree of Master of science (Audiology) of the student (Registration No: 15AUD003). 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 "**Correlation between vHIT and caloric test in individual 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

I hereby declare that this dissertation entitled "**Correlation between vHIT and caloric test in individual with Auditory Neuropathy Spectrum Disorder**" is the result of my own study under the guidance of **Dr.Sujeet Kumar Sinha**, Reader Audiology, Department of Audiology, All India Institute of Speech and Hearing, Manasagangothri, Mysore and has not been submitted earlier to any other university for the award or any other Diploma or Degree.

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Abstract

Aim: The present study was designed to understand the correlation between vHIT and caloric test in individual with ANSD.

Method: Two groups of subjects with total number of 30 individuals participated in the study. Group I comprised of 15 individuals, 7 males and 8 females, n= 30 ears with the age range of 17 to 38 years (mean age= 25.2yrs) with ANSD. Group II comprised of 15 individuals, 10 males and 5 females in the age range of 18 to 24years (mean = 22.1yrs) with normal hearing sensitivity. All the participants underwent a detailed case history, Maryland dizziness questionnaire administration, pure tone audiometry, immittance and reflexometry, OAEs, ABR vHIT and caloric tests.

Results: In vHIT, VOR gain was significantly higher in normal individuals compared to that of individuals with ANSD for all the canals. Also, there was an elevation in VOR gain asymmetry for all three planes of semi-circular canals in individual with ANSD than normal individuals. Presence of corrective refixation saccades was found to be 100% in individuals with ANSD which was absent in normal hearing individuals. However, no significant correlation was present between VOR gain and duration as well as VOR gain asymmetry and duration for any of the three orthogonal planes. Also, there was no significant association between the VOR gain of any of the canals and degree of hearing loss in individuals with ANSD. In caloric test, all the normal hearing individuals had normal caloric response. Prevalence of hypoactive response was present in most of the individuals with ANSD followed by few having normal response for right warm stimulation only. However, there was no significant association in either of the bithermal

stimulation and degree of hearing loss for both the ears in individuals with ANSD. Also, no significant association was seen between any of the bithermal stimulation and lateral canals.

Conclusions: To conclude, a large percentage of individuals with ANSD have been found to have associated vestibular dysfunction as well. However the lack of positive correlation between the vHIT and caloric test results in these individuals suggests the ability of two tests in assessing two different frequency domains of the same semi-circular canal. Also as vHIT assesses all six semicircular canals, it can be taken as the complementary test in vestibular test battery approach to further diagnose individuals with ANSD to have 'auditory neuropathy only' or 'auditory-vestibular neuropathy' as recommended by Kaga (2009).Therefore the use of both the vestibular tests, vHIT and caloric should be utilized in these individuals as both the tests are complementary to each other, evaluating different components of semi-circular canals and its innervations.

Chapter 1

INTRODUCTION

Auditory neuropathy spectrum disorder (ANSD) is the term being used across the age group ranging from infants to adults with most of the characteristic criteria fulfilled such as: presence of otoacoustic emission or cochlear microphonics in ECohGs resembling preserved OHC's functioning; absence of auditory evoked brainstem response and acoustic reflex displaying the lack of synchronous firing of 8th cranial nerve; affected speech identification score that doesn't correlate with the pure tone average (PTA) of the individual and the variable degree as well as pattern of hearing loss (Sheykholeslami, Kaga, Murofushi, & Hughes, 2000; Y. Sininger & Starr, 2001; Arnold Starr, 2001; A Starr et al., 1991; Arnold Starr, Picton, Sininger, Hood, & Berlin, 1996; Zeng, 2006).

As the auditory and vestibular receptors (first order neuron) of 8th cranial nerve are intrinsically linked with the common pathway, the frequent pathophysiological demyelination at periphery level of 8th cranial nerve are likely to involve both auditory and vestibular divisions leading to neuropathy on both the sides (Buetti & Luxon, 2014). However immense literature on auditory neuropathy (C. I. Berlin, 1999; Davis & Hirsh, 1979; Kowalski, Rasheva, & Zakrzewska, 1991; U. A. Kumar & Jayaram, 2006; Scaioli, Pareyson, Avanzini, & Sghirlanzoni, 1992; Sheykholeslami et al., 2000; Arnold Starr et al., 1996; Tang, McPherson, Yuen, Wong, & Lee, 2004) and rare description of vestibular neuropathy (Fujikawa & Starr, 2000; K Kumar, Singh, Sinha, Bharti, & Barman, 2007; Sheykholeslami et al., 2000; Sheykholeslami, Schmerber, Habiby Kermany, & Kaga, 2005; Arnold Starr et al., 1996) can be due to the slow progressive development of the pathology, likely, not much expressed due to the effective vestibular

compensatory mechanism, and more consideration given on proprioception and cerebellar functioning for the imbalance problem in individual with ANSD (Melgaard & Zilstorff, 1979).

Few reports are available in the literature regarding the presence of vestibular dysfunction in individual with ANSD. Presence of horizontal nystagmus on lateral gaze, absence of caloric response, abnormal/absent vestibular evoked myogenic responses (VEMP) response suggest the presence of generalized peripheral pathologic changes at the level of vestibulocochlear nerve(Kaga et al., 1996; K Kumar et al., 2007; A Starr et al., 1991). Furthermore, abnormal Romberg's, Mann's and Fukuda stepping tests response in eyes closed condition correlates with the earlier reports suggesting the involvement of neuropathologic condition at the vestibular branch of 8th cranial nerve(Sheykholeslami et al., 2005). Hence these studies explains the existence of affected peripheral vestibular branch and normal central vestibular connections in individual with ANSD.

1.1 Need for the study

1.1.1 Need of vestibular study in Auditory Neuropathy Spectrum Disorder (ANSD)

The prevalence of ANSD differs across the studies and age groups. Study by Davis and Hirsh (Davis & Hirsh, 1979) reported that 1 in every 200 children with hearing impairment are prone to have ANSD. However, only 4% of children with permanent hearing loss to have ANSD(C. I. Berlin, 1999). Similarly, it was reported that 0.02% of every infants kept in NICU are prone to have auditory neuropathy(Y. Sininger & Starr, 2001). In Indian perspective, the prevalence of ANSD is around 0.54% or 1 in every 183

individuals with sensorineural hearing loss(U. A. Kumar & Jayaram, 2006). These individual with ANSD have either stable, fluctuating or progressively worsening hearing sensitivity influenced by temperature sensitivity, auto-immune disorders etc. giving rise to the variable range of speech perception. Few of them have speech identification scores (SIS) correlating with the degree of hearing loss while others, its disproportionate with poor SIS percentage(Rance, Cone-Wesson, Wunderlich, & Dowell, 2002; Rance, McKay, & Grayden, 2004) and even affected timing cues(Rance et al., 2004).

Moreover along with auditory impairments, the signs of vestibular impairments such as dizziness, tinnitus, unsteadiness etc. have often been reported by the individuals with ANSD. The prevalence of vestibular impairment varies across the studies. In the retrospective study on 50 individuals with ANSD, 53% of them were found to have vestibular dysfunction with hypoactive caloric response (Samaha & Katsakas, 2000). Study by Fujikawa and Starr (2000) reported 64% (9 out of 14) of the individuals with ANSD to have abnormal vestibular response in caloric test. 22% of the individual with ANSD also have bilateral vestibular impairments(Zingler et al., 2007). Conversely, the other study by Sheykholeslami et al. (2000) reported the complete absence of cervical VEMP response in all of the 6 individuals with ANSD. Likewise Palla, Schmid-Priscoveanu, Studer, Hess, and Straumann (2009) reported the reduced vestibulo-ocular reflex in 81% of the individual with axonal ANSD and 63% of the individual with demyelinating ANSD. Likewise K Kumar et al. (2007) reported around 80% of the ears with ANSD to have abnormal vestibular evoked myogenic response. Moreover higher incidence of vestibular abnormalities have been reported by Sinha, Shankar, and Sharanya (2013) where out of 11 individuals with ANSD, 100% of them had absent

oVEMP response and 90.9% with absent cVEMP response. Another study by Sujeet, Niraj, Animesh, Rajeshwari, and Sharanya (2014) on 26 individuals with ANSD reported 96.15% of them with abnormal cVEMP response and 86.53% of them with bilateral hypoactive caloric response suggesting the involvement of both inferior and superior vestibular nerve branches in these individuals. Therefore considering these vestibular impairments, one can predict the adverse consequences of getting imbalanced and falls, mostly with visual cues cut off in the individuals with ANSD.

The demyelinating changes at the level of vestibular branch of 8th cranial nerve brings the variation in functioning of sensory vestibular end organs such as saccule, utricle and semicircular canals which can result in adverse consequences. Therefore, to make the rehabilitation effective, the differential diagnosis of the condition and the precise detection of the lesion area should be done. Earlier studies have reported affected functioning of saccule (Akdogan, Selcuk, Ozcan, & Dere, 2008; Kaushlendra Kumar, Sinha, Singh, Bharti, & Barman, 2013; Sheykholeslami et al., 2005) and utricle (S. Sinha, A. Barman, N. Singh, G. Rajeshwari, & R. Sharanya, 2013) in the individual with ANSD. Also the caloric test resulted in affected horizontal semicircular canal functioning secondary to neuropathic changes in 8th cranial nerve(Abdel-Nasser, Elkhayat, Khalil, & Mahmoud, 2006; Akdogan et al., 2008; Fujikawa & Starr, 2000; Kaga, 2009; Sheykholeslami et al., 2000; Arnold Starr et al., 2003; Arnold Starr et al., 1996).

However, well- known caloric test detects the functioning of only two horizontal SCCs at very low and brief frequency range of around 0.002–0.004 Hz which is beyond the frequency range the semicircular canals experience in day to day life (Perez & Rama-

Lopez, 2003). Also the shortcomings of it is lack of assessment of all three planes, the semicircular canals experience in everyday life.

1.1.2 Need of study in vHIT

Earlier reports on head impulse test (HIT) which checks for the integrity of vestibular system, monitoring the vestibular ocular reflex revealed the presence of saccades whenever the head was stimulated towards the affected peripheral side (Halmagyi & Curthoys, 1988; McCaslin, Jacobson, Bennett, Gruenwald, & Green, 2014). At present, the need of the objective tests for assessing dynamic functions of semi-circular canals has been accomplished with the recent advancement of non-invasive, new instrument known as video head impulse test (vHIT), developed by Halmagyi and Curthoys (Halmagyi & Curthoys, 1988).

The vHIT is based on the principle of head impulse test (HIT) using same amplitude and high acceleration head impulse with light weighted goggles consisting of a gyroscope to measure the angular head movements and also checks the pupil of the individual with high speed eye position digital camera (Baloh, Honrubia, & Sills, 1977; Böhmer, Henn, & Suzuki, 1985; H. G. MacDougall, Weber, McGarvie, Halmagyi, & Curthoys, 2009). With the brief but high velocity head impulses in the yaw and pitch axes, vHIT examines all six SCCs separately (H. G. MacDougall, L. A. McGarvie, G. M. Halmagyi, I. S. Curthoys, & K. P. Weber, 2013; Migliaccio & Cremer, 2011).

The vHIT has been authenticated by simultaneous comparison with the scleral search coil across both the healthy as well as pathological vestibular population such as Meniere's disease (McCaslin et al., 2014), vestibular neuritis (M. Bartolomeo et al.,

2014), vestibular migraine (McGarvie et al., 2015) and also in case of benign paroxysmal positional vertigo (Blödow et al., 2014b) with good sensitivity and specificity. Therefore, vHIT can be the important tool in test battery approach in evaluation of the peripheral vestibular system in individual with ANSD.

1.1.3 Need for correlation between caloric with vHIT test

A very considerable clinical literature are described by the fact that the caloric test measures the functioning of the lateral semicircular canal at 0.003 Hz (Perez & Rama-Lopez, 2003) however, vHIT measures VOR gain of all six semi-circular canals at a high frequency stimulus (H. G. MacDougall et al., 2013).

In reference to the air caloric test, vHIT is found to be relatively insensitive to the peripheral vestibular disorder where most of the individual with canal paresis indicated by caloric test were still found to be normal. Nevertheless the presence of abnormal vHIT for the patients with complete hypofunction of caloric response (S. L. Bell et al., 2015) which is consistent in findings with (Hamish Gavin MacDougall, Leigh Andrew McGarvie, Gabor Michael Halmagyi, Ian Stewart Curthoys, & Konrad Peter Weber, 2013) where abnormal vHIT response were observed in individuals with unilateral vestibular deafferentation secondary to vestibular schwannoma surgery makes the test useful in the vestibular test battery.

This can help us to know the sensitivity and specificity of both the tests in assessing the individual with ANSD.

1.2 Aim of the Study

The present study aimed at correlation between vHIT and caloric test in individual with ANSD.

1.3 Objectives of the study

- To assess VOR gain function in the individual with ANSD.
- To check for refixation saccades which may be covert or overt in nature in the individual with ANSD.
- To check for any correlation with degree of hearing loss for Caloric and v-HIT test in individual with ANSD.
- To find out correlation between the Caloric and v-HIT test results in individual with ANSD.

Chapter 2

REVIEW OF LITERATURE

Auditory neuropathy spectrum disorder (ANSD) is a degenerative condition first termed by Arnold Starr et al. (1996), characterized by the presence of otoacoustic emissions (OAEs)/ cochlear microphonics (CM) indicating intact outer hair cell functioning and affected auditory brainstem responses (ABR) signifying abnormal auditory nerve firing.

Clinical profile of Individuals with ANSD

2.1 Onset and course

ANSD is found to be seen in infancy, adolescence or early adulthood of life (Rance et al., 2004). Another study by Kumar and Jayaram (2006) suggested the mean age of onset of the condition to be 16 years of age where 59% of the cases (out of 61 individuals with ANSD) were found to have the condition in early adulthood of 14 to 24 years old. The severity of the neuropathic symptoms of the condition is reported to be unpredictable i.e it can stay still, resolve, alter or deteriorate over the period of time. Moreover 81% of the cases reported the conditions to get worsen over the period. Similar result was reported by Masuda and Kaga (2011) where they studied the changes in hearing and vestibular functions with aging in 3 female patients with ANSD. Participants were examined with speech discrimination tests, DPOAE, ABR, damped rotational chair test, caloric test and VEMPs. Thus, authors reported the effect of aging in pure tone

audiometry, speech audiometry and vestibular functioning in individuals with auditory neuropathy.

2.2 Prevalence

Study by Davis and Hirsh (1979) reported the prevalence of ANSD in 1 in every 200 children with hearing loss with consistent audiological pattern. Moreover Stein et al. (1996) reported higher prevalence of ANSD in neonates. 4% (4 out of 100) of neonates at high risk were found to having ANSD on extensive assessment. However other by Psarommatis, Tsakanikos, Kontorgianni, Ntouniadakis, and Apostolopoulos (1997) revealed 2 out of 102 neonates (1.9%) at high risk (as per guideline of JCIH) were found to have featured with typical ANSD. The prevalence of this neuropathic condition has been reported differently across different studies as 40% in NICU infants with hearing impairment (Rea & Gibson, 2003), 10% in newborns (Y. S. Sininger, 2002), 1% in deaf schools (Foerst et al., 2006) and 0.54% in adults with SNHL (U. A. Kumar & Jayaram, 2006). Rance et al. (1999) studied on 5,199 babies with risk of having hearing loss and was found to have ANSD prevalent in 0.23% or 1% in every 433 individuals on long term extensive assessment.

2.3 Pathophysiology of ANSD

Most of the conditions in ANSD are found to have lesion at the level of auditory nerve itself. Hence the condition was named by Arnold Starr et al. (1996) based on the symptoms wherein 80% of the cases studied were found to have abnormality in other peripheral nerve along with hearing impairment. ANSD can be accompanied with

variable level of axonal loss, myelin sheath damage or both resulting in disrupted neural synchrony and abnormal auditory functioning.

Demyelination of 8th cranial nerve results in enhanced membrane capacitance and reduced membrane resistance giving rise to delayed firing and propagation of action potentials (McDonald & Sears, 1970; Pender & Sears, 1984; Rasminsky & Sears, 1972). Also the degrees of demyelination across auditory nerve fibres may vary among one another such that it results in variance of speed of neural conduction affecting the neural synchrony. Therefore these demyelinated auditory nerve fibers are repetitively activated giving rise to the condition named conduction block where there is a prolonged conduction time followed by intermittent or total block in transmission of action potentials (Rasminsky & Sears, 1972).

In case of axonal loss, rather than reduction in conduction speed, it gives rise to reduction in amplitude of compound action potential of auditory nerve fibres resulting in diminished auditory brainstem response.

2.4 Audiological profile

2.4.1 Degree and configuration of hearing loss.

Previous reports on ANSD have suggested disparity in hearing loss across individuals varying from normal to profound hearing loss (Davis & Hirsh, 1979; Rance et al., 2004; Arnold Starr, Sininger, & Pratt, 2000; Worthington & Peters, 1980). Arnold Starr et al. (2000) reported 31% of ears with mean thresholds of less than 35dBHL, 39% of ears with mean thresholds between 35dBHL to 70dBHL and 30% of ears with more than 70dBHL in a group of 67 individuals diagnosed with ANSD. Also based on pattern

of hearing loss, 41% of the ears had rising low frequency loss, 5% with U shaped configuration, 11% with sloping high frequency loss, 29% with irregular saw tooth configuration and 5% with tent shaped loss having peak at 2 KHz.

The fluctuation in hearing threshold is peculiar feature in ANSD which was previously reported by Rance et al. (1999) where 5 out of 14 individuals with significant fluctuations in threshold by 20dBHL approximately. Also study by U. A. Kumar and Jayaram (2006) revealed audiometric configurations of 61 individuals with ANSD where 26 of them had peaked audiogram (mostly at 2KHz), 11 with flat, 11 with rising, 8 with saucer shaped and 3 with sloping pattern bilaterally. Also the degree of hearing loss was reported to fluctuate from mild to severe loss.

2.4.2 Acoustic Reflex Threshold

Konrádsson (1996) reported the presence of acoustic reflex in the ear detected as having ANSD when the probe stimulation was given in normal functioning contralateral ear. This is suggestive of the presence of primary disruption mechanism in acoustic reflex loop in afferent pathway (Tibesar & Shallop, 2005). Moreover, even though middle ear reflexes are absent in individuals with ANSD for acoustic stimulation, its preserved for non-acoustic signals (Arnold Starr et al., 1998).

Typically, one of the triad features of ANSD includes elevated/absent acoustic reflex both ipsilaterally and contralaterally (U. A. Kumar & Jayaram, 2006; Arnold Starr et al., 1998; Xu, Liu, Lian, Yang, & Tang, 2002). Study by Shivashankar, Satishchandra, Shashikala, and Gore (2003) did auditory profile in 24 individuals with primary auditory neuropathy. Hence it was revealed absent middle ear reflexes in individuals with ANSD.

Similarly the study by C. I. Berlin et al. (2010) reported affected acoustic reflex thresholds at all the frequencies measured. Out of 136 subjects with ANSD tested, only three of them had reflex lesser than or equal to 95dBHL.

2.4.3 Otoacoustic Emissions (OAE) and Cochlear microphonics (CM)

Earlier studies reported the presence of CMs in 4 subjects for as long as 5msec duration (A Starr et al., 1991; Arnold Starr et al., 1998) came up with the correlation regarding the presence CMs and OAEs where it was reported that in the individuals with TEOAE present, the mean amplitude of CMs was found as 0.46μv and in case of absent TEOAE, the mean amplitude of CMs was found as 0.38μv.

Similar result has been reported earlier by Deltenre et al. (1999) where two children were diagnosed to have ANSD in their infancy using the criteria given by Arnold Starr et al. (1996) but with period of time OAEs got vanished out. Moreover the presence of CMs were still intact with similar large amplitude and increased latency as examined earlier except in one case where subtle morphological variation was seen.

One of the classsic triad characteristic of ANSD is the preserved outer hair cell functioning. Cochlear microphonics are classically robust in nature and present for several msec suggesting the normal functioning outer hair cells (C. I. Berlin, 1999; Santarelli & Arslan, 2002). Similar result has been reported by Rance et al. (1999) where there was presence of CMs in 33 ears studied and only 16 ears with OAEs. Moreover in this study they had considered the presence of CMs as one of the primary criteria in identifying ANSD as OAEs could be affected by subtle middle ear conditions. Also they considered the hypothesis that the existence of significant OHCs dysfunction could result

in absence of OAEs, however CMs would be preserved as it's contributed by the inner hair cells.

Few studies have reported absence of robust amplitude OAEs over a period of time which could be due to the exposure of auditory system to conditions such as middle ear disease or use of amplification devices (Arnold Starr et al., 2000). In this retrospective study of 67 patients with ANSD, it was reported that auditory neuropathy varies in several measures such as age of onset, etiology, presence of peripheral neuropathy which brings variation in behavioral and physiological functioning in auditory domain.

In the study by C. Berlin, Hood, and Rose (2001), robust amplitude OAEs were reported which was similar in finding as by U. A. Kumar and Jayaram (2006) where mean amplitude of Transient evoked otoacoustic emissions (TEOAE's) was higher (16dBSPL) as compared to normal hearing individuals (11.5dBSPL). Hence this phenomenon was described as an outcome of lack of efferent suppression in individuals with ANSD.

In the review article by Rance (2005), they have reported approximately 7% of children with sensorineural hearing loss and significant number of adults to have common behavioral and physiological profile of ANSD. The study attempted to explain the physiological variation in generation of CMs and OAEs. They have described as the ability of the outer hair cells to polarize and depolarize, giving rise to generation of CMs. However in case of OAEs, if the functioning of outer hair cell is impaired such that the mechanical cochlear processes gets affected resulting in the absence of OAEs.

2.4.4 Auditory Brainstem Responses (ABR)

Physiologically, it reveals the dysfunction of auditory nerve in individuals with ANSD. Therefore the abnormal/absent response can be due to the decreased number of neural components required for the elicitation of the response. Also it can be because of the asynchronous firings or prolonged refractory period among the nerve fibers. It has been reported that even the dys-synchrony in neural firing by fraction of msec can result in abnormal ABR with diminished waves (A Starr et al., 1991).

Typically ABR are found to be absent in ANSD and in case of its presence, are severely affected in terms of morphology, amplitude and latency. Arnold Starr et al. (2000) reported 73% of individuals with the absence of ABR, 21% with abnormal wave V in terms of latency and amplitude, 6% with presence of wave III and V with subtly affected morphology, latency and amplitude. Similarly, Arnold Starr (2001) reported 21% of the studied ANSD population revealed the presence of wave V alone. However its amplitude was reduced in comparison to the normal hearing individuals (0.01μv in ANSD compared to 0.51 μv in normal hearing individuals) and latency was prolonged.

2.4.5 Speech perception.

Arnold Starr et al. (1996) reported variation in word recognition score from 0% to 92% in 8 individuals with ANSD. Affected speech perception has been reported extensively in individuals with SNHL where it correlates with the PTA. However in case of ANSD, this becomes exceptional as the speech scores are disproportionate with the PTA (Arnold Starr et al., 2000). Difficulties in speech perception in these individuals could be due to the asynchronous firing of auditory nerve resulting in abnormal temporal

coding (Rance et al., 2004; Zeng, 2006). Also in the retrospective study of 60 individuals with ANSD, it was found to have un-proportionate speech identification scores that vary from 0% to 90%. Also the speech identification scores were found to have correlation with pure tone at 250Hz and 500Hz. This was ascribed as the difference in physiological basis in coding low and high frequency sounds where low frequency thresholds could suggest the degree of temporal dis-integrity in auditory system which us helps in understanding the extent of difficulty in speech perception by an individual with ANSD (U. A. Kumar & Jayaram, 2006).

Conversely, there are individuals with ANSD having speech perception deficits well correlated with the particular degree of SNHL. In the study by Y. Sininger and Oba (2001) and Arnold Starr et al. (1996), they have reported around 25-30% individuals with ANSD were found to have speech identification scores in proportion to the degree of hearing loss in quiet situation that could be due to the subtle neuropathic involvement in these individuals in comparison to the rest of the population studied.

2.5 Vestibular tests

2.5.1 Vestibular test findings in individuals with ANSD

Few of the studies on degenerative peripheral neuropathies such as neurosarcoidosis were reported to have vestibular neuropathy as well where comorbid demyelination of auditory, vestibular and facial nerves were found to be present resulting in the degeneration of associated end organs. In the single case study of 32 year old man with sarcoidosis, histological findings revealed degeneration of cochlear and labyrinthine neuroepithelium and stria vascularis. With audiological criteria fulfilled as ANSD, these

individuals were found to have no nystagmus on caloric stimulation suggesting bilateral dysfunction lateral semicircular canals(Babin, Liu, & Aschenbrener, 1984; Von Brevern, Lempert, Bronstein, & Kocen, 1997). Also another single case study of 45 years old female with chronic inflammatory demyelinating polyneuropathy where noted with having limb weakness, postural difficulty, foot numbness and oscillopsia. Client underwent various tests such as clinical examination, bithermal caloric, rotatory chair testing, dynamic posturography etc. It was found to have reduced caloric response on bithermal stimulation suggesting of vestibular dysfunction in degenerative peripheral pathologies.(Frohman, Tusa, Mark, & Cornblath, 1996).

Preliminary studies on vestibular functioning in ANSD was reported by Arnold Starr et al. (1996) where out of 10 individuals studied, 3 of them had horizontal nystagmus on lateral gaze and 2 had no response in caloric test performed. Along with auditory related changes, these individuals had neuropathic changes in vestibular functioning also which led authors to conclude the generalized neuropathy condition where both the components of vestibulocochlear nerve are affected. Also the study by Kaga et al. (1996) reported the slight engrossment of vestibular organs and brainstem in individuals with auditory nerve disease where the two individuals were examined to have absence of nystagmus in ice water caloric test, normal results in positioning, positional and central tests.

Study by Konrádsson (1996) reported the four children fulfilling the criteria of ANSD without any complaint of vestibular dysfunction. These children underwent vestibular evaluations which included bithermal caloric test, smooth pursuit test, saccadic test and optokinetic test where it showed normal test results for all of them suggesting the

presence of pure ANSD affecting auditory system only. Also Akdogan et al. (2008) reported normal caloric response in all 3 children with ANSD studied. In addition, Fujikawa and Starr (2000) studied vestibular functioning in 14 individuals with ANSD. Caloric tests in all these individuals revealed vestibular neuropathy as a late manifestation to the condition in individuals with ANSD. Also, Jen, Baloh, Ishiyama, and Baloh (2005) reported a child with Dejerine-Sottas syndrome (HMSN type III) with canal paresis in caloric tests with complete absence of Vestibulo-ocular reflex suggesting bilateral vestibular dysfunction.

Fujikawa and Starr (2000) studied vestibular functioning in 14 individuals with auditory and peripheral neuropathies when symptoms related to vestibular dysfunction were absent. All the individuals were detected to have ANSD bilaterally and eight of them were found to have concomitant peripheral neuropathies too. Vestibular dysfunction was reported in 9 out of 14 subjects where 7 of them had concomitant peripheral neuropathies. In the vestibular abnormal group 5 had no response and 4 had asymmetrical response on ENG/VNG test. All these individuals were found to have normal saccadic response. The optokinetic test, gaze test and sinusoidal tracking test performed in 5 subjects revealed response within normal range. These results concluded that in some cases of degenerative peripheral neuropathies, there can be involvement of vestibular nerve as well. Out of 2 individuals with hypoactive caloric response without peripheral neuropathies, one of them had temperature sensitive auditory neuropathy resulting in demyelination of 8th cranial nerve and the other one was found to have isolated auditory neuropathy. Hence the study revealed the variation to the degree of neuropathic

involvement of vestibular nerve in individuals with auditory neuropathy as well as peripheral neuropathies.

Study by Sheykholeslami et al. (2000) recorded VEMP in 3 individuals with ANSD which was done to understand the effect of the pathology on the sacculo-collic pathway. Rectified VEMP recordings were obtained at 500Hz air conduction tone burst stimuli where there was absent VEMP response for all the individuals which was suggestive of dysfunction of inferior vestibular nerve along with auditory nerve in these individuals. Moreover, it was reported that the extent of inferior vestibular nerve dysfunction was as variable as the auditory related features and findings in these individuals with ANSD.

Arnold Starr et al. (2003) studied vestibular functioning in family with ANSD type hearing loss comorbid with peripheral neuropathy. The study revealed histopathological alterations in vestibular nerves which was analogous to the clinical findings such as lack of eye movements and no sensation of imbalance in caloric test in two of the individuals of the family. These neurotic findings suggested the neural loss in the vestibular system joining lateral semicircular canals and Scarpa ganglion. Moreover distorted beaded appearing vestibular nerve due to the fragmentation of myelin sheath with gaps approximately the diameter of nerve fiber was seen signifying its incomplete remyelination. These histopathological features are suggestive of the hypoactive response in caloric test. Also, the beaded appearance observed in the distal than the proximal portion of the vestibular nerve may indicate the presence of pathology limited within the distal portion rather than invading central portion of the vestibular system. This can explain the reason behind normal functioning of individuals with ANSD in gaze, saccade

and optokinetic tests (Abdel-Nasser et al., 2006; Sheykholeslami et al., 2000; Sheykholeslami et al., 2005; Arnold Starr et al., 2003). This suggests the presence of ANSD in absence of peripheral neuropathy with range of variability in vestibular functioning.

Single case study by Sheykholeslami et al. (2005) reported the VEMP response to be in right ear and absent in left ear. Similarly, it was found to have normal caloric test results for both the ears, therefore, suggesting unilateral sacculo-collic neuropathy with bilateral ANSD. Hence it was concluded that the vestibular involvement may vary from normal functioning to single portion of the vestibular apparatus (saccule/utricle and their innervations) dysfunction as well as complete vestibular areflexia.

Another study by Sheykholeslami et al. (2005) examined 3 individuals with ANSD having complaint of balance problem where it was found to have abnormal response for Romberg, stepping and Mann tests in eyes closed condition. Also there was absence of spontaneous nystagmus confirming no involvement of central vestibular tract. Ice water caloric test done in right ear revealed horizontal nystagmus without vertigo in only one individual. However there was hypoactive response for other individuals. It was concluded that in case of isolated auditory neuropathy, both the vestibular portion of 8th cranial nerve and its innervations can be affected. In case of individuals with unprogressed isolated auditory neuropathy, there can be involvement of both auditory and vestibular system, hence concluding to use the term “cochlear neuropathy” for the condition with the involvement of auditory portion of 8th cranial nerve and its innervations.

Further studies in individuals with ANSD revealed the condition to be prevailed irrespective of any association with other peripheral neuropathy. Study by Abdel-Nasser et al. (2006) reported the vestibular functioning in 50 individuals with ANSD where 30% of them had bilateral reduced caloric response, 14% had bilateral absent caloric response suggesting bilateral extensive vestibular lesion. Also out of 50 individuals with ANSD, only 18% of them revealed the presence of dizziness and other imbalance features. All the individuals showed lack of spontaneous, positional, positioning and gaze nystagmus in evaluation. Also normal saccade velocity, latency and accuracy was observed in oculomotor test. Optokinetic and eye tracking evaluations revealed normal test results. These detail inspection on peripheral and central portion of vestibular system revealed the presence of normal central vestibular connections thereby restricting the pathology within peripheral vestibular connections. Other study by Kaga (2009) reported hypoactive response on ice water stimulation used in caloric test, hence these individuals were identified as individuals with 'auditory-vestibular neuropathy'. However three of the indiviuals with ANSD were found to have normal vestibular findings, thus were termed as 'auditory neuropathy only'.

Out of 20 ears, 16 ears evaluated in individuals with ANSD reported abnormal of cervical VEMPs response. It was revealed that out of 20 ears tested, 80% of them had either absent or prolonged response with reduced amplitude (K Kumar et al., 2007). Hence K Kumar et al. (2007) came up with the term "acoustic neuropathy" for indicating those individuals with features related to auditory nerve only and "vestibulo-acoustic neuropathy" for indicating those individuals with features related to vestibular nerve along with acoustic nerve. In this study, probable reason for the absence of VEMPs was

ascribed to the fact that both the cochlear and vestibular portions are the division of same nerve fiber bundle known as 8th cranial nerve or vestibulocochlear nerve. Therefore, neuropathic condition in one of the branch (auditory branch) of the 8th cranial nerve resulting in other branch (vestibular branch) as well.

The study by Akdogan et al. (2008) on 3 children in the age range of 4-5years with ANSD where cervical VEMP recordings were obtained. It was reported that there was absence of replicable VEMP responses in 2 out of 3 children which was in combination to normal caloric test results in all 3 individuals. Hence, author suggested the usage of detailed vestibular test battery so as to rehabilitate children for their deficits timely.

Sazgar, Yazdani, Rezazadeh, and Yazdi (2010) made an attempt to understand saccule and its neural functioning in individuals with ANSD where 8 individuals in the age of 21 to 45 years with bilateral ANSD were taken for the study. Each individuals underwent VEMPs testing where it was found that out of 16 ears, 3 ears had normal responses while all other ears had abnormal responses containing absent replicable VEMPs response in 4 ears and absent response in 9 ears. Hence, the study suggested the presence of bilateral manifestation of the neuropathy and its slow progression. Also, it was reported that central compensatory mechanism decreases in response of vestibular end organs that was linked with hearing loss.

Also in the study by S. Sinha et al. (2013) reported the study on 3 individuals with ANSD where there was hypo-functional caloric test result along with absent cVEMP response. 2 out of 3 individuals with ANSD had asymptomatic vestibular dysfunction. Two subjects were found to have deviations present in clinical tests of stability

suggesting the presence of superior and inferior vestibular nerve dysfunction in these individuals. Also it was reported regarding the development of compensatory features over time to overcome the disability due to vestibular neuropathy.

Another study by S. K. Sinha, K. Shankar, et al. (2013) carried out the study to examine the functioning of vestibular nerve in individuals with ANSD. 11 individuals with ANSD participated in the study where cVEMP and oVEMP were performed in these individuals. It was found that 100% of these participants had absent oVEMP and 90.0% of them had absent cVEMP. Hence the authors suggested a high incidence of vestibulopathy in individuals with ANSD and therefore the need to include vestibular test battery for assessing suspected ANSD candidates.

Sujeet et al. (2014) studied on 26 individuals with ANSD who underwent cVEMP and caloric tests. It was revealed that there was absence of response in cVEMP and bilateral hypo-functional response in caloric tests in most of the individuals suggesting the involvement of both superior and inferior portion of vestibular nerve in individuals with ANSD and there was no association between caloric test results with degree and configuration of hearing loss.

Study by Singh, Sinha, and Barman (2016) intended in examining the otolith modulated functioning in individuals with ANSD. Static group comparison of 31 healthy individuals as control group and 31 individuals with ANSD were taken for the study. Both cVEMP and oVEMP were administered at 500Hz tone bursts where less than 20% response was present for both the potentials in experimental group. Also there was significant prolonged inter-peak and later peaks latency and significant decreased amplitudes in ANSD individuals than the control groups. Also the abnormal or absent

responses indicated the dysfunction of superior and inferior vestibular nerves in these individuals. Therefore, the authors strongly debated for the need to include vestibular test battery for assessing suspected ANSD candidates.

To conclude, neuropathic condition of auditory nerve may also comprise vestibular nerve. The variations seen in audiological findings across individuals with ANSD can be parallel to the vestibular findings with a huge unevenness. Moreover, the neuropathic condition of vestibulocochlear nerve is limited within peripheral vestibular system than invading central oculomotor system.

2.6 Video Head Impulse Test findings in different populations

2.6.1 Video Head Impulse Test (vHIT)

Earlier study by Aw et al. (1999) reported the presence of saccades when the high velocity head movement was towards the lesioned peripheral side. This technique is known as Head Impulse Test (HIT) which was initially used in order to examine the individuals who are not able to give response or in coma patients. HIT examines the Vestibulo-ocular reflex pathway wherein patient are instructed to gaze at the target even while the jerk is given to head in pitch, yaw and roll axis. Therefore in case of a lesion at the level of SCC, it affects VOR. However, the central mechanism acts in order to maintain the gaze in a stationary target with compensatory saccades. These saccades generated during the head jerk are virtually difficult to observe with naked eyes (Black, Halmagyi, Thurtell, Todd, & Curthoys, 2005; Weber et al., 2008).

This inability of HIT is solved by a recent advancement of Video Head Impulse Test which works in the same principle as HIT at same amplitude and high acceleration.

vHIT is capable of measuring overt and covert saccades (which cannot be detected by naked eye). Moreover patient needs to wear a light weighted goggles consisting of a gyroscope to measure the angular head movements and also checks the pupil of the individual with high speed eye position digital camera (Baloh et al., 1977; Böhmer et al., 1985; H. G. MacDougall et al., 2009).

2.6.2 vHIT in younger individuals

vHIT has been reported to be beneficial over other vestibular tests in examining various clinical conditions related to semicircular canals in both children and adults. The study was done where 33 individuals with vestibular pathologies (age range less than 20 years) underwent vestibular tests such as rotatory chair test, caloric test and vHIT. Out of all three tests, percentage of abnormalities given by caloric test and rotatory chair test were lesser in comparison to vHIT where VOR gain was found to be reduced in all of the participants with vestibular pathologies. Hence it was concluded as vHIT being the important tool in diagnosis of vestibular conditions in children (Hamilton, Zhou, & Brodsky, 2015).

Hulse, Hormann, Servais, Hulse, and Wenzel (2015) reported a study of video head impulse test in 55 children (age range 3 to 16 years). The standard group comparison was done in the study where group I consisted of children without any features of vestibular related issues and group II constituted individuals with pathological equilibrium development. The reduced VOR gain was observed in children in group II which gave evidence to the authors to conclude vHIT as an important screening tool to check for any vestibular dysfunction in children.

Ross and Helminski (2016) Studied the reliability of horizontal and vertical vHIT and maturational effect on angular VOR gain function and peak head velocities of canals in normal children and adolescents. 28 typically developing children with age range of 4.33–17.25 years were taken foe the study vHIT was administered in all the individuals. Hence it revealed vHIT as a reliable tool in examining canal function in pediatric population using high velocity head impulse. However in children, it was observed to have asymmetric compensatory eye movements when the head velocities were more than 100 degrees/s in vertical canals.

2.6.3 vHIT in elderly individuals

Study by Matino-Soler, Esteller-More, Martin-Sanchez, Martinez-Sanchez, and Perez-Fernandez (2015) in 212 individuals with no history of any neurological or vestibular impairment reported. vHIT was measured in these individuals in yaw axis where mean VOR gain was found to be 1.06 ± 0.07, with compensatory saccades present in only 52 individuals. The age range of individuals with compensatory saccades present was significantly higher after 71 years of age. However the reduced VOR gain was correlated with head impulse velocity where with increase in head velocity, VOR gain reduced. Hence it was concluded that the VOR gain was found to be stable till the age of 90 years and later, it started declining.

The normative study by Mossman, Mossman, Purdie, and Schneider (2015) in 60 normal individuals (age range of 20 to 80 years) with no history of any neurological or vestibular impairment. vHIT administered on horizontal plane retrieved a mean VOR gain of 0.97. Authors also reported the reduced VOR gain with advancement of age in

these individuals. However, McGarvie et al. (2015) reported vHIT response in horizontal plane 80 healthy individuals in decade age bands starting from 10 years till 90 years of age where it got revealed that the VOR gain reduced at high head velocity and was unaffected with increment in age.

2.6.4 vHIT in Vestibular neuritis

Quick, non-invasive vHIT has been recommended by M. Bartolomeo et al. (2014) in detecting individuals with vestibular neuritis. The study included 29 individuals with vestibular neuritis who were studied in follow up of 1-3 months. Caloric and vHIT evaluations were performed in follow up. It revealed complete recovery of 31% of the individuals with vestibular neuritis in caloric test and 51.8% in vHIT. Hence it concluded that even being fast and easier in operation, vHIT lags in sensitivity in comparison to caloric for individuals with moderate problem.

Schubert, Mantokoudis, Xie, and Agrawal (2014) reported VOR gain as one of the measure to differential diagnose stroke and vestibular neuritis. The study was done on 26 individuals with acute vestibular symptoms where MRI scan revealed individuals with onset of stroke to have lesion at anterior inferior cerebellar artery (AICA) or posterior inferior cerebellar artery (PICA). 16 out of 26 individuals had vestibular neuritis, 7 out of 26 had PICA and 3 out of 26 had AICA. vHIT done on all these individuals showed ipsi-lesioned and contra-lesioned mean VOR gain as: AICA stroke (0.84, 0.74); PICA stroke (0.94, 0.93) and vestibular neuritis (0.52, 0.87). Out of the three conditions, VOR gain was symmetrical in PICA stroke revealing bilateral normal VOR pathway whereas it was

heterogeneous in AICA stroke. Moreover in case of vestibular neuritis, it was found to be asymmetrical suggesting unilateral vestibulopathy.

vHIT has been reported as an important tool in detecting individuals with vestibular neuritis. Study was done by Merchant et al. (2015) in 32 individuals with vestibular neuritis where air conducted 500 Hz tone burst was used in measuring cVEMP and oVEMP and also, vHIT was done in all 3 planes. Hence it was concluded that the use of three tests helped in differentially diagnosing four types of vestibular neuritis i.e. entire vestibular neuritis, inferior vestibular neuritis, superior vestibular neuritis and ampullary vestibular neuritis. In case of partial inferior and superior vestibular nerve involvement, it resulted absent oVEMP response. Similarly, Taylor et al. (2016) studied on 43 individuals with vestibular neuritis who underwent canal plane video head impulse test, air conducted cervical and bone conducted ocular VEMP. Hence, out of 43 patients, 16 of them were retested after 6-12 months follow up period and 8 of them recovered. Therefore the study concluded vestibular neuritis might often have lesion in both vestibular nerve branches, therefore only horizontal vHIT assessment could detect superior nerve lesion in these individuals. Hence one should do VEMP and posterior vHIT in check for any inferior nerve involvement also.

As caloric test measures semicircular canal functioning in low frequency in contrary to vHIT, both tests need to be used in complementary to each other. Redondo-Martinez et al. (2016) studied on 20 individuals with neuritis where caloric test and vHIT were performed in these individuals. Gain asymmetry was calculated and compared with canal paresis. However there was found to be no correlation between the tests. Hence authors concluded that two tests can to be used for complementing each other rather than

substituting as they show different frequencies of vestibule- ocular reflex. Similar conclusion was made by Zellhuber, Mahringer, and Rambold (2014) where study was done to understand the correlation between horizontal vHIT and bithermal caloric test responses in individuals with unilateral vestibular neuritis. However, no linear correlation was achieved in gain asymmetry and ipsilesional gain of vHIT with unilateral weakness of caloric test suggesting the use of both the tests in assessing individuals suspected with vestibular anomalies.

2.6.5 vHIT in Meniere's disease

Zulueta-Santos, Lujan, Manrique-Huarte, and Perez-Fernandez (2014) reported vHIT as an vital diagnostic device in detecting involvement of semicircular canals in individuals with Meniere's disease. 36 patients with Meniere's disease were taken for the study where vHIT was done in all three planes. Out of all, 12 of them (33.3%) were found to have normal semicircular canals functioning, other 12 individuals (33.3%) were found to have at least one of the semicircular canals functioning in affected ears, 11 individuals (30.5%) had abnormal results in at least one of the semicircular canals functioning in affected and unaffected ears and 1 individual (2.9%) was found to have abnormal semicircular canals functioning in unaffected ear. Mostly, the affected result was observed in coupled superior semicircular canal of the unaffected ear and posterior semicircular canal of the affected ear. Hence it was concluded that the gain reduction reflected the duration of the disease onset and degree of hearing loss.

Another study by Chen et al. (2015) reported vHIT as an useful tool in detecting Meniere's disease where they studied on 30 individuals with unilateral Meniere's disease

and classified them on the basis of severity of the condition. Therefore on vHIT evaluation, it was found to have no significant difference between normals and individual with mild Meniere's disease, however, there was significant difference between normals and individual with severe Meniere's disease.

vHIT can be a useful tool in assessing and estimating prognosis in individual with Meniere's disease treated with gentamycin. Marques, Manrique-Huarte, and Perez-Fernandez (2015) studied on 31 individuals with unilateral Meniere's disease. All the individuals were given dose of intra-tympanic gentamycin and were followed for 6 to 7 months. Hence vHIT was done both prior and after the dose given. It was found that all the individuals were having reduced VOR gain response in all planes in post treatment condition. The VOR gain had reduced by 26%, 47.9 % and 35.8 % in horizontal, superior, posterior semicircular canals respectively. Thus it was concluded that the dose of intra-tympanic gentamicin bringing change in VOR gain suggested the act of the dose in short term control over vertigo attacks in these individuals.

2.6.6 vHIT in Vestibulopathy

Eza-Nuñez, Fariñas-Alvarez, and Perez-Fernandez (2014) reported vHIT as an important tool in diagnosing vestibulopathy. 50 individuals with unilateral vestibulopathy were studied. Horizontal vHIT assessment done on these individuals revealed refixation compensatory saccades seen in 21 out of 30 individuals on the affected side. However VOR gain was found to be 0.91. Hence it was concluded that vHIT on individuals with complaint of dizziness suggested the presence of peripheral vestibulopathy.

Superficial siderosis (SS) is a pathological condition related to cerebellar ataxia and SNHL which results due to excess iron composition on central nervous system surfaces. This condition might also result in damage to vestibulo-cochlear nerve giving rise to vestibulopathy bilaterally. Kang, Lee, Kim, Cho, and Lee (2015) reported single case study of 60 year old individual with a severe gait disorder, oscillospia and progressive hearing loss in both ears. It was diagnosed as superficial siderosis after MRI evaluation. vHIT administered revealed reduced VOR gain of 0.55, 0.45 and 0.59 in horizontal, posterior and anterior semicircular canals respectively. Hence authors concluded that vHIT can be important tool in documenting vestibulopathy in superficial siderosis.

2.6.7 vHIT in Benign paroxysmal positional vertigo (BPPV)

vHIT can be useful in diagnosis of individuals with BPPV. Study was done on 12 individuals with idiopathic BPPV where vHIT elicited normal VOR gain function in all six semicircular canals and no signification variation was seen in between the same canals between the ear for individuals with BPPV where canalolothiasis was present in superior semicircular canal. However gain asymmetry was found to be variant for each pairs of canals Perez-Fernandez, Martinez-Lopez, and Manrique-Huarte (2014).

Mangabeira Albernaz and Zuma (2014) reported single case study of 42 years old individual with BPPV due to otoconia plugged in horizontal canals. vHIT and cVEMP were administered before and after the maneuvers. It was found that VOR gain had reduced and improved after 2 days of the maneuvers administered. VEMP was found to

be absent before exercise but was identifiable after 30 days of maneuver applied. Hence vHIT can be useful in measuring the efficacy of treatment maneuvers for BPPV.

2.6.8 vHIT in Other disorders

Magliulo et al. (2015) studied the usefulness of vHIT assessment in detecting vestibular anomalies in individuals with Usher's syndrome. 15 individuals with Usher's syndrome underwent vHIT assessment where 10 out of 15 individuals were found to have abnormal VOR gain. However reduced VOR gain could be due to poor visual capacity or vestibular anomaly. Hence it need to be answered in further research.

Also, Zhang et al. (2015) studied vHIT in 48 individuals with central vestibular pathology and 47 with peripheral vestibular pathology. Out of 23 ears with Meniere's disease, 21 of them were found to be affected, 6 with sudden hearing loss, 2 with vestibular neuritis, 8 patients with vestibular dysfunction, 5 with delayed endolymphatic hydrops and 4 with vestibular schwannoma were found to have decrement in VOR gain. Also 35 out of 48 individuals with central vertigo that constituted 7 individuals with posterior cerebral circulation ischemia, 17 individuals with dizziness and vertigo, 6 individuals with cerebral infarction and others (18 individuals) were found to have abnormal vHIT response. Also, abnormal VOR response rate in central vertigo patient was 72. 9% and 95. 7% in peripheral vertigo. Hence abnormal vHIT can illustrate the sign of peripheral or central pathology.

Study by Neupane et al, (2017) reported the usefulness of vHIT in assessing 30 individuals with motion sickness where there was normal VOR gain between the normal and individual with motion sickness. However, the presence of higher asymmetry ratio in

vHIT and cVEMP plus refixation saccades to maintain the gaze in vHIT in individuals with motion sickness suggested the presence of vestibular pathology in these individuals.

Considering all above studies in different clinical populations, vHIT is found to have good sensitivity in assessing and estimating the changes in peripheral vestibular functioning. VOR gain, VOR gain asymmetry and refixation saccades are taken as the different parameters in distinguishing vestibular malfunctioning in these clinical populations from that of the normative. However, even if many of the vestibular disorders are well studied with vHIT, ANSD remains unexplored. Hence in this study, it has been attempted to understand the effect of ANSD in different parameters of vHIT.

Chapter 3

METHOD

The study was conducted with an aim of understanding the correlation between vHIT and caloric test in individual with ANSD. To fulfil the aim, following methods were adopted.

3.1 Participants

Two groups of subjects with total number of 30 individuals participated in the study.

- Group I comprised of 15 individuals, 7 males and 8 females, n= 30 ears with the age range of 17 to 38 years (mean age= 25.2yrs) with ANSD.
- Group II comprised of 15 individuals, 10 males and 5 females in the age range of 18 to 24years (mean = 22.1yrs) with normal hearing sensitivity.

3.1.1 Participant selection Criteria:

3.1.1.1 Individuals with ANSD (Group I)

- All participants were diagnosed to have bilateral ANSD based on the criteria of poor speech in noise scores, absence of ipsilateral and contralateral acoustic reflex response, presence of otoacoustic emissions/ cochlear microphonics and absence of auditory brainstem response.
- The participants were identified to have sensorineural hearing loss.

- No restriction regarding the degree of hearing loss was considered as there could be large variability in individual with ANSD (U. A. Kumar & Jayaram, 2006).
- The participants with "A" type tympanograms and no history or presence of middle ear pathology were taken for the study.
- Neurological examination excluded the presence of space occupying lesion in all the participants.
- None of the participants had undergone vestibulotoxic medication and none complained any other illness earlier to the testing.

3.1.1.2 Normal Hearing Individuals (Group II)

The subjects included in the control group was age matched to the experimental group and fulfilled the following criteria.

- The participants were examined to have normal hearing sensitivity (≤ 15 dBHL) at octaves from 250 Hz to 8000 Hz for air conduction and from 250 Hz to 4000 Hz for bone conduction.
- The participants had 'A' type tympanogram with both ipsilateral and contralateral reflexes in immittance evaluation.
- No history or presence of any relevant middle ear pathology
- No history or presence of any vestibular related abnormalities.
- No history or presence of any neurological problems.
- None of the participants had undergone vestibulotoxic medication and none complained any other illness earlier to the testing.

3.2 Test instrument

All the tests were performed within noise permissible criteria of ANSI S3.1 (1991) in an acoustically treated room.

3.3 Instrumentation

1. Calibrated GSI audiometer (GSI VIASYS Healthcare, Wisconsin, USA) was used to perform threshold estimation (pure tone audiometry and speech audiometry) for ruling out any hearing loss components in both the groups to meet within inclusion criteria. Calibrated TDH 39 headphones (Telephonics, 815 Broad Hollow Road, Farmingdale, New York 11735) for AC threshold and calibrated B-71 bone vibrator (Radioear, KIMMETRICS, 22050 Mohawk Drive, Smithsburg, MD 21783) for BC threshold were used.
2. Calibrated GSI Tympstar Immittance (GSI VIASYS Healthcare, Wisconsin, USA) meter was used to measure tympanometry with a probe tone frequency of 226 Hz. The same equipment was used for measuring ipsilateral as well as contralateral reflexometry at 500, 1000, 2000, and 4000 Hz.
3. Calibrated ILO 292 V-6 (Otodynamics Ltd., Hatfield, Herts, UK) system was used to measure otoacoustic emissions.
4. Calibrated IHS (Intelligent Hearing System) Smart EP (3.94 USBez) system (Intelligent Hearing System, Florida, USA) was used to administer click evoked auditory brainstem response with ER-3A insert phones (Etymotic Research, Inc., 61 Martin Lane, Elk Grove Village, IL 60007, USA).

5. GN Otometrics manufactured v-HIT (GN Otometrics, Taastrup, Denmark) instrument along with laptop running Otosuite software and frenzel glasses were used for measuring VOR gain function of six semi-circular canal.
6. Videonystagmography (BioMed Jena GmbH, LutherstraBe 148, 07743 Jena, Germany) was used for performing caloric test in both the groups.

3.4 Procedure:

All the participants underwent various audiological and vestibular evaluations which are listed as follows:

3.4.1 Clinical Case History and Questionnaire Administration

A detailed case history was taken for all the participants in the study regarding the nature and onset of the hearing loss and attacks of vertigo (if any). Information on medical history and associated problems (if any such as neurological, visual conditions) were obtained. Also, Maryland Dizziness Questionnaire was administered on each individual of both the groups. Out of 5 sections of the questionnaire, only the 2nd section which was related with the features of dizziness was administered.

3.4.2 Pure Tone Audiometry:

Using the modified Hughson and Westlake procedure(Carhart & Jerger, 1959), air conduction threshold with the TDH 39 headphones and bone conduction thresholds with B-71 bone vibrator were obtained for octave frequencies from 250 to 8000 Hz and 250 to

4000 Hz respectively to investigate the hearing sensitivity of the each participants. Pure tone average (PTA) was calculated by taking mean at 500 Hz, 1 kHz, 2 kHz and 4 kHz.

3.4.3 Impedance audiometry:

Tympanometry and reflexometry were done to rule out any pathology at middle ear or auditory nerve level. Tympanometry was done at 226 Hz probe tone and acoustic reflex threshold was elicited for both ipsilateral and contralateral stimulation at 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz.

3.4.4 Otoacoustic emission:

Transient evoked OAEs were recorded in double walled sound treated room with 260 pairs of clicks stimuli. Probe fit was assessed by examining the stimulus spectrum and was adjusted to produce minimal ringing and flat spectrum. The stimulus was presented at 80 dB peak SPL. The OAEs were considered as present if the OAE SNR was greater than 6 dB for 3 consecutive frequencies. OAEs were recorded in non-linear mode.

3.4.5 Auditory Brainstem Response

Participants were placed in a reclining chair and cleaned at both the mastoids (M1, M2), and forehead (Fz) with skin abrasive followed by the vertical electrode placement. Also intra-electrode impedance and inter-electrode impedance were maintained < 5 kΩ and < 2 kΩ respectively. It was performed with making participants relaxed with reduced extraneous body movements.

Auditory brainstem response was recorded with 1500 sweeps of click stimulus through insert earphones. 90dBnHL click stimulus (rarefaction polarity) at 11.1/s repetition rates and the response was recorded in ipsilateral mode in single channel with minimum of two replications of the waveform in 12msec analysis time. The waveform response are recorded with bandpass filter between 100Hz to 3000Hz.

3.4.6 vHIT:

With laptop running Otosuite vestibular software, Video Head Impulse test was administered in well-lit room. Frenzel glasses with clean attached face cushion were tightened appropriately to avoid slippage such that the camera can track participants' pupil movement. The vHIT instrument had two laser pointers projected onto the wall, placed at the distance of 1 metre from participant seated adjustable for the purpose of calibration. Therefore the instrument was calibrated with instruction to track laser pointer moving alternatively at two targets without moving the head. Once calibrated, it was instructed to fix the gaze in front at a dot target even when the head thrust was given to achieve the VOR gain at different planes. The head thrust of 40 times was given for each planes (pitch, roll and yaw planes) at an angle of 10-20 degree in randomized order. The VOR gain for all six semi-circular canals was measured with the help of high speed digital infrared camera attached to the instrument. During the testing, head was accelerated sufficiently such that the semi-circular canal on the side of stimulation got excited while the other side led to inhibition of afferents. The presence of vestibular lacunae with total or partial loss of semicircular canal functioning led to unmatching of eye velocity curve to that of head velocity curve and gave rise to refixation saccades i.e.

overt and covert saccades to preserve the gaze stability(DeLong & Jacobson, 2013; Mossman et al., 2015; J. N. Patterson, A. M. Bassett, C. M. Mollak, & J. A. Honaker, 2015).

3.4.7 Caloric test:

VNG instrument was used for recording the response of caloric test. With the placement of the inverting electrode at 1.5cm lateral to the outer canthi of the left eye, non- inverting electrode at 1.5 cm lateral to the outer canthi of the right eye and ground at forehead, single channel recording was performed. Prior to the recording of each participants, calibration of the VNG instrument was carried out.

Table 3.1: Protocol for recording caloric test

Parameters	**Setting**
Notch filter	On
Gain	Gain of the incoming signal was adjusted such that 10 mm deflection of recording pen represents 200 µv of corneoretinal potentials
Number of channels	1.00
Band Pass Filter	0.1 Hz to 30 Hz
Electrode Montage	Non-inverting electrode (+): outer canthus of the right eye Inverting electrode (–): outer canthus of the left eye ground electrode: lower forehead

3.5 Analysis

3.5.1 Analysis of vHIT

Based on the Hex plot, the vHIT response was analysed where the VOR gain of each of all six semi-circular canals and the refixation saccades (if any) at the time of head thrust i.e. covert saccade, after the head thrust i.e. overt saccade were represented. Also effect of duration of ANSD in the results of vHIT was analysed. Also the age of the individuals and effect of duration of ANSD in the results of vHIT were analysed.

3.5.2 Analysis of Caloric test

The cumulative frequency was taken in consideration to be denoted on the butterfly chart. The four response waves achieved with bi-thermal stimulation were calculated and the cumulative frequency was achieved. The cumulative frequency was calculated with the recordings divided into 10sec intervals. The three adjacent intervals were taken which had maximum nystagmus beats. Hence, the cumulative frequency is the total number of beats in 30sec time period after the stimulation. Thus cumulative frequency was measured for both the groups in the study. The data of four conditions from the normal hearing group was employed to define the normative range of the Hail-Stoll butterfly chart. This was followed by plotting the cumulative frequencies for the four recordings achieved from the individuals with ANSD on Hail-Stoll butterfly chart.

With the help of Hail-Stoll Butterfly chart, the caloric responses were interpreted as normal, hypoactive or hyperactive based on its location i.e. within, below or above the normal limits of culmination frequency respectively. Also with digits as normal = 0; hypoactive = 1 and hyperactive = 2, the responses were labeled.

3.5.3 Statistical Analysis

The entire statistics was done with the help of IBM SPSS 20.0 software. Following statistics were done-

1. Shapiro Wilk test was done to check the normality of the data.
2. Descriptive statistics was done to find out the mean and the standard deviations for VOR gain, VOR gain asymmetry.
3. Independent sample t test was done to compare the VOR gain and VOR gain asymmetry between the normal individuals and individuals with auditory neuropathy spectrum disorders.
4. Pearson correlation test was done to check the Correlation between VOR gain and duration of six semi-circular canals in individual with ANSD.
5. Pearson's correlation was performed to understand the relation between the VOR gain and VOR gain asymmetry with the duration of disease in individuals with ANSD.
6. Chi square test was administered to understand the association of VOR gain with the degree of hearing loss in specific ear in individuals with ANSD.
7. Chi square test was performed to understand the association of caloric test result and the degree of hearing loss in specific ear in individuals with ANSD.
8. Chi square test was administered to check the association of caloric test result with the VOR gain of lateral canals in specific ear in individuals with ANSD.

Chapter 4

RESULTS

The present study was carried out with an aim to understand the correlation between vHIT and caloric test in individual diagnosed with auditory neuropathy spectrum disorder. To check the functioning of vestibular system with vHIT and caloric test, individuals with auditory neuropathy spectrum disorder were compared with their normal counterparts. For vHIT, Vestibulo-ocular gain response, asymmetry ratio and corrective refixation saccades were measured. With the usage of bi-thermal stimulation, caloric tests measured the functioning of lateral semi-circular canals.

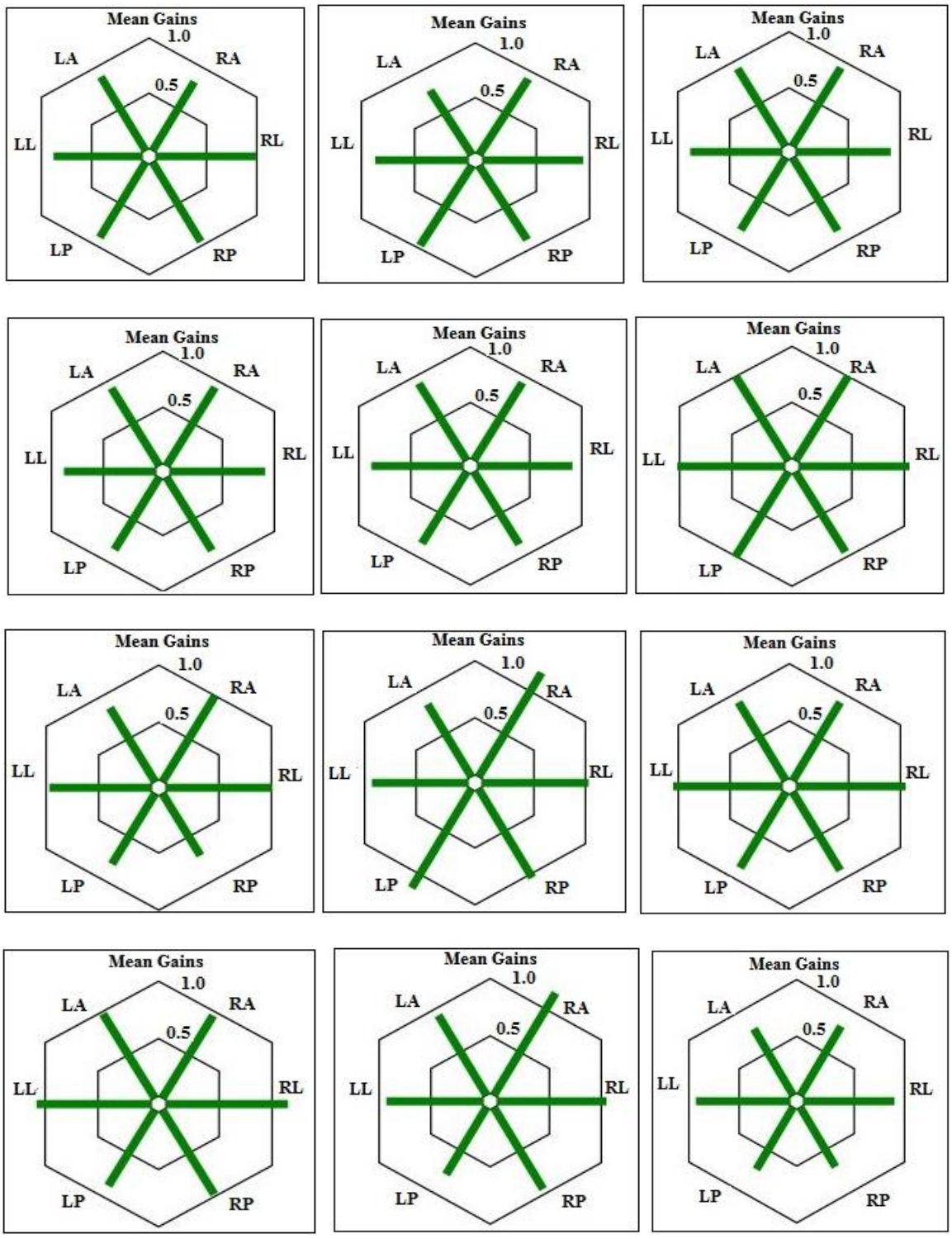
Therefore to obtain the aim of the study, relevant data achieved from both the groups having 15 individuals with ANSD and 15 normal hearing individuals was undertaken for descriptive statistics and correlation using IBM SPSS v22 software.

4.1 Video Head Impulse test results in individuals with Auditory Neuropathy Spectrum Disorder

4.1.1 VOR gain

VOR gain was calculated for three planes of semi-circular canals. For individuals with ANSD and normal hearing individuals, descriptive statistics was performed to estimate the mean and standard deviation of VOR gain for both the groups in all three planes of the semi-circular canals. The hex plot representing VOR gain of vHIT responses recorded from each individuals of both the groups are given in Figures 4.1.1.1

and 4.1.1.2 where the VOR gain lesser than 0.8 was taken as abnormal(Jessie N Patterson, Alaina M Bassett, Clairissa M Mollak, & Julie A Honaker, 2015).



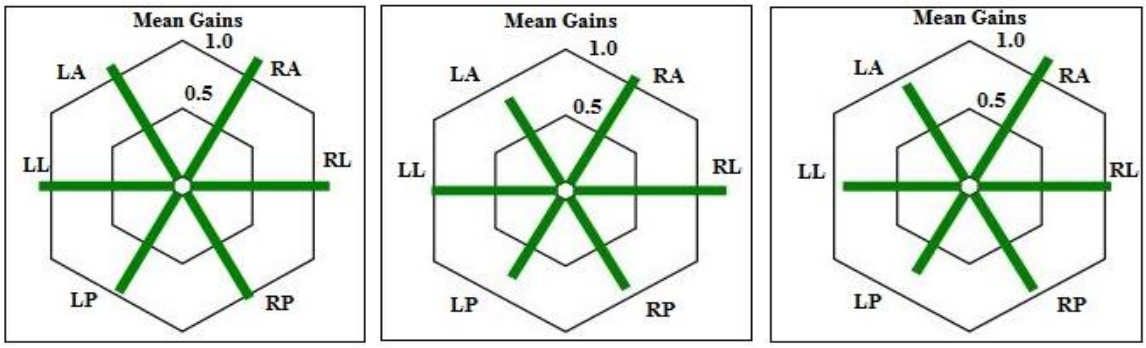
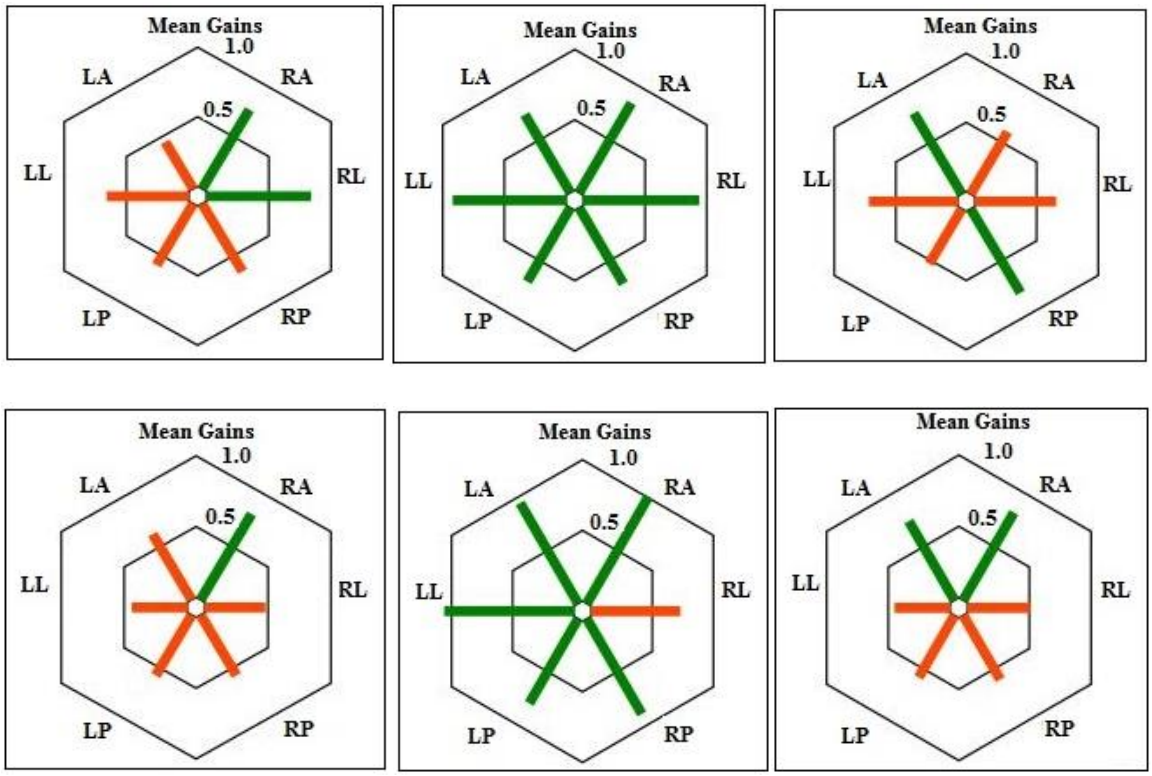


Figure 4.1.1.1: Hex plot of VOR gain measured with video head-impulse test response in three different planes of semi-circular canals in 15 normal hearing individuals.

Figure 4.1.1.1 included the Hex plot of VOR gain values in 15 normal hearing individuals. As the VOR gain of all the semi-circular canals was more than 0.8, it was considered to be within normal limits.



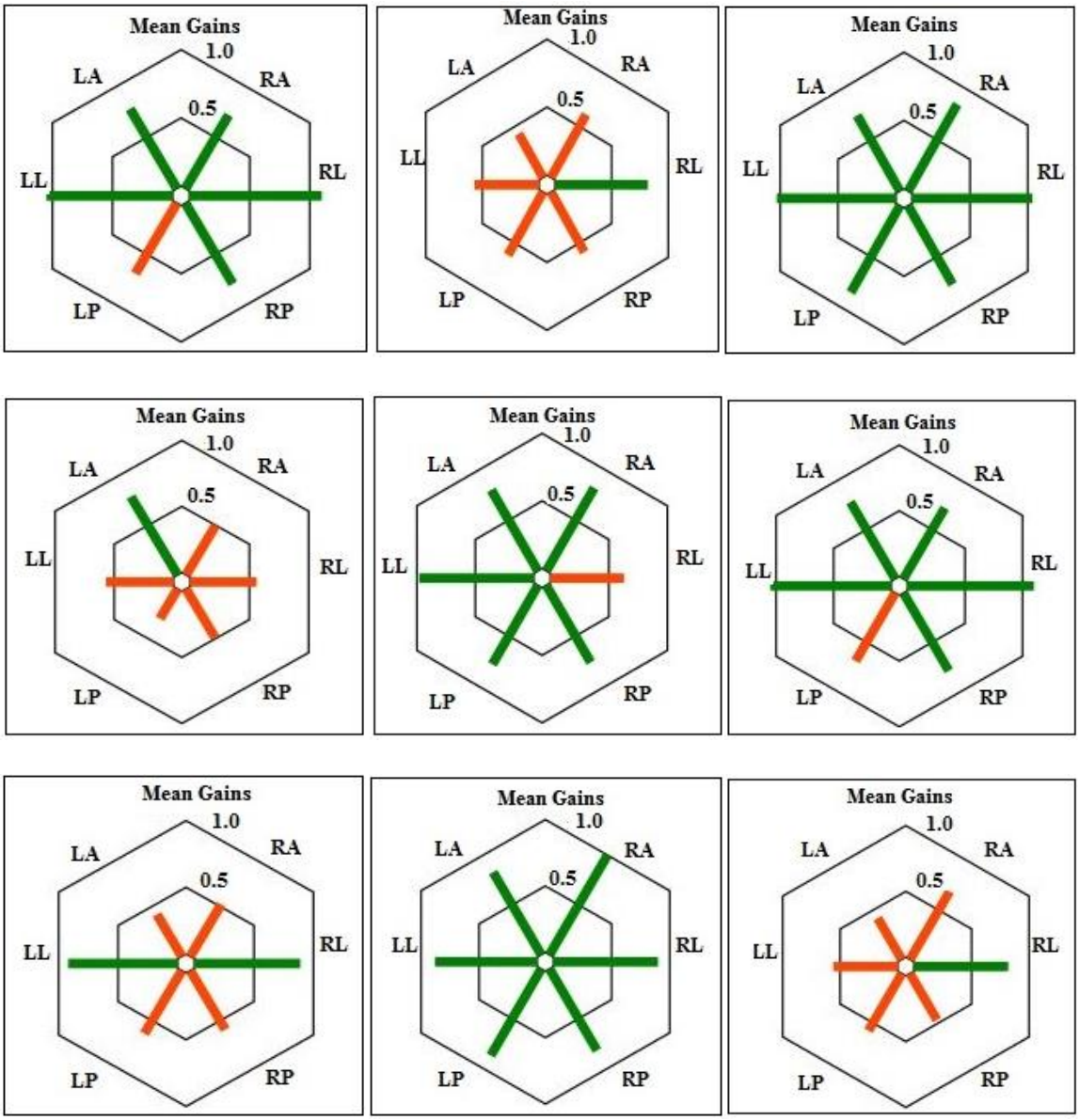


Figure 4.1.1.2: Hex plot of VOR gain measured with video head-impulse test response in three different planes of semi-circular canals in 15 individual with ANSD.

Figure 4.1.1.2 shows the Hex plot of VOR gain values in 15 individuals with ANSD. Most of the individuals were found to have reduced VOR gain (<0.8) in one or more than one semi-circular canals. However, three of the individuals with ANSD had normal VOR gain in all six semi-circular canals.

Descriptive statistics was done for both the groups to measure the mean and standard deviation of VOR gain in all three planes. Table 4.1.1.1 represents the descriptive statistics of VOR gain for all three planes of semi-circular canals in both the groups.

Table 4.1.1.1: Mean and standard deviation of VOR gain for all six semi-circular canals for both the groups.

Planes	**ANSD Individuals (N= 15)**		**Normal Individuals (N=15)**	
	$\bar{x}$	**SD.**	**$\bar{x}$**	**SD.**
Left Lateral (LL)	0.76	0.06	0.95	0.02
Right Lateral (RL)	0.77	0.05	1.00	0.02
Left Anterior (LA)	0.69	0.05	0.89	0.03
Right Posterior (RP)	0.70	0.04	0.89	0.04
Left Posterior (LP)	0.66	0.04	0.88	0.03
Right Anterior (RA)	0.77	0.04	0.97	0.04

Note: N= number of participants; $\bar{x}$ = Mean; SD = Standard Deviation.

From Table 4.1.1.1, it can be observed that the mean VOR gain is reduced in individuals with ANSD than in normal individuals for all six semi-circular canals. It can be observed the same in figure 4.1.1.3.

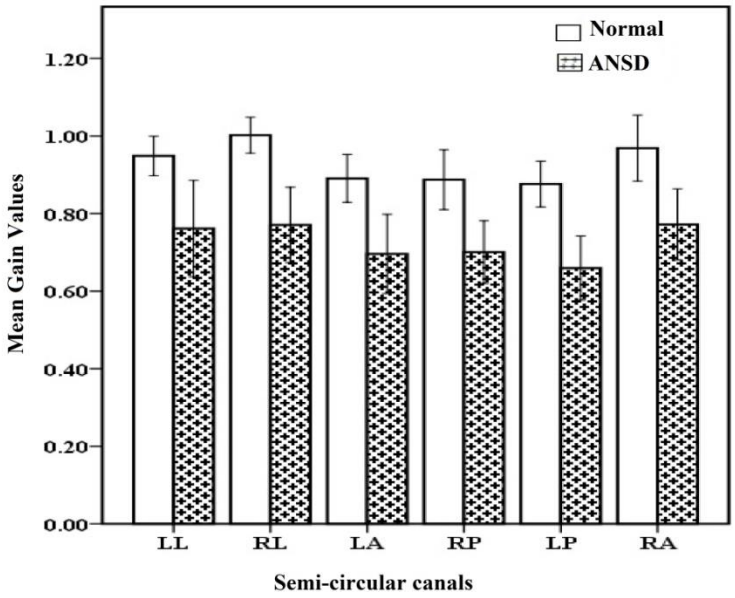


Figure 4.1.1.3: The graph represents mean and standard deviation of VOR gain values for all six semi-circular canals in both the groups.

To find out if there exists any significant difference of VOR gain for all six canals between the groups, Independent sample‘t’ test was administered. The table 4.1.1.2 represents the independent sample test statistics.

Table 4.1.1.2: Independent sample test results for parameters of VOR gain between the groups.

Planes	**Independent sample ‘t’ test between ANSD and normal Individuals**	
	t	**p**
Left Lateral (LL)	2.99	0.01
Right Lateral (RL)	4.61	0.00

Left Anterior (LA)	3.50	0.002
Right Posterior (RP)	3.58	0.001
Left Posterior (LP)	4.58	0.001
Right Anterior (RA)	3.37	0.002

It can be seen from table 4.1.1.2 that the VOR gain was significantly higher in normal individuals compared to that of individuals with ANSD for all the canals.

4.1.2 VOR gain asymmetry

Descriptive statistics was administered for both the groups to measure the mean and standard deviation of VOR gain asymmetry in all three planes. Table 4.1.2.1 represents the mean and standard deviation of the VOR gains asymmetry of coplanar axis of semi-circular canals in both the groups.

Table 4.1.2.1: Mean and standard deviation of VOR gain asymmetry of all three planes in both the groups.

Planes	**ANSD Individuals (N= 15)**		**Normal Individuals (N=15)**	
	$\bar{x}$	**SD.**	**$\bar{x}$**	**SD.**
Lateral	16.93	12.31	7.87	1.31
RALP	19.67	8.67	8.53	1.20
LARP	17.86	12.00	6.27	1.50

Note: N= number of participants; $\bar{x}$ = mean; SD = standard deviation; LARP= Left Anterior Right Posterior; RALP= Right Anterior Left Posterior

It can be seen from table 4.1.2.1 that there was an elevation in VOR gain asymmetry for all three planes of semi-circular canals in individual with ANSD than normal individuals. The same can be seen in figure 4.1.2.1.

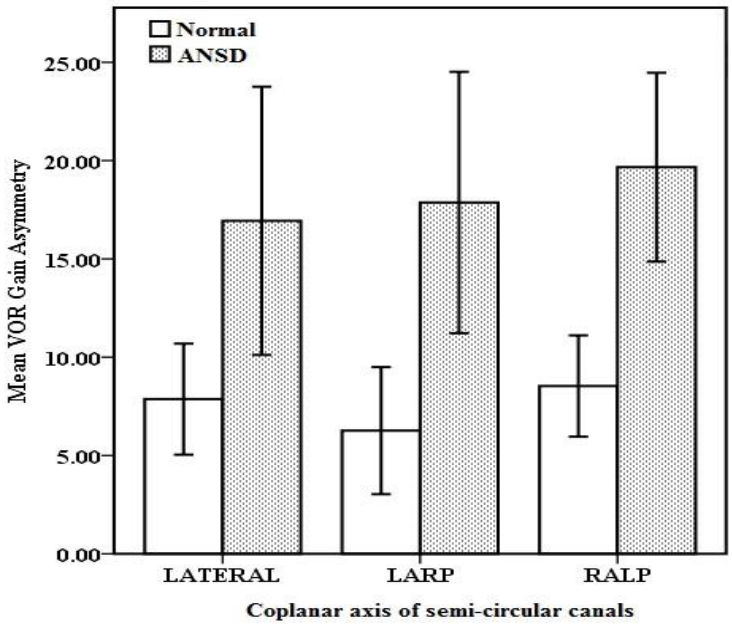


Figure 4.1.2.1: The graph represents mean and standard deviation of VOR gain asymmetry in all three planes of semi-circular canals for both the groups.

Also, to check if there exists any significant difference of VOR gain asymmetry in all three planes of semi-circular canals between the groups, Independent sample ‘t’ test was administered. The table 4.1.2.2 represents the independent sample test statistics.

Table 4.1.2.2: Independent sample‘t’ test results for asymmetry of VOR gain in three planes between the groups.

VOR gain asymmetry	Independent sample ‘t’ test between ANSD and normal Individuals	
	t	**p**
Lateral	2.64	0.01
RALP	4.39	0.00
LARP	3.37	0.002

It can be seen from figure 4.1.1.2 that all the planes of VOR gain asymmetry was significantly different in individuals with ANSD compared to that of normal individuals.

4.1.3 Refixation saccades

The corrective refixation saccades i.e. covert and overt saccades were studied in both the groups where it was observed to be present in individuals with ANSD. However it was found to be absent in normal hearing individuals. Table 4.1.2.3 represents the presence of the refixation saccades in each of the semi-circular canals in individuals with ANSD. Similarly, figure 4.1.3.1. shows the presence and absence of refixation saccades in different canals measured in one of the individuals with ANSD.

Table 4.1.3.1: Refixation saccades in each of the semi-circular canals present in the individuals with ANSD.

Semi-circular Canals	Covert Saccade	Overt Saccade	Covert + Overt	None
Left Lateral	3	2	7	3
Right Lateral	5	0	9	1
Left Anterior	2	0	1	12
Right Anterior	4	0	0	10
Left Posterior	2	1	2	10
Right posterior	2	0	3	9

From the table 4.1.2.3, it can be observed that the only covert saccade condition was present in all six semi-circular canals in individuals with ANSD. Similarly the both covert and overt saccades condition was found in all six canals except right anterior (RA). However the only overt saccade condition was present in left lateral (LL) and left posterior (LP) canals. Also the presence of saccades were witnessed more in number for lateral semi-circular canals. There were few individuals with ANSD in whom there were no saccades in different canals. None of the normal hearing individuals had saccades.

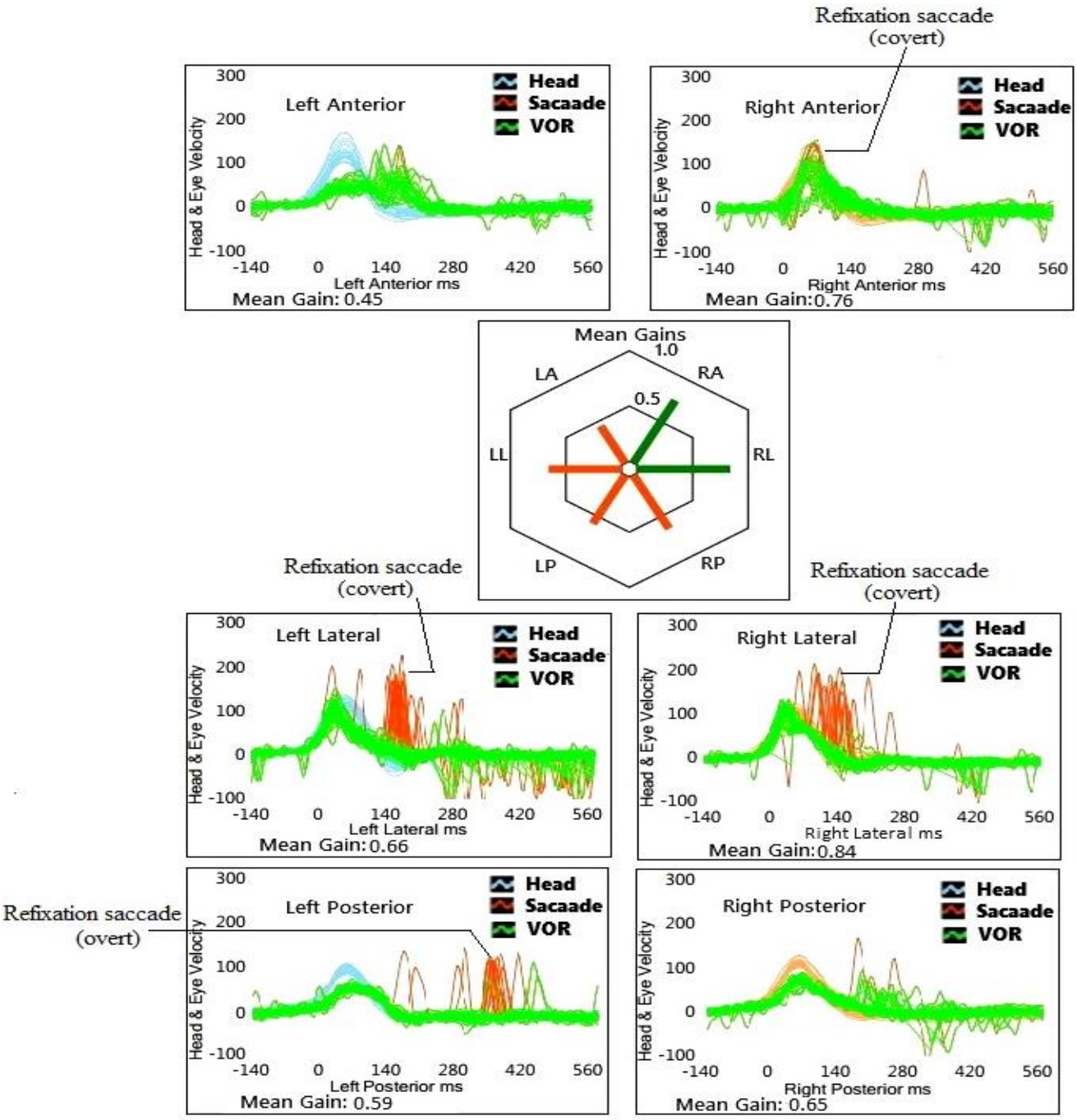


Figure 4.1.3.1: Video head-impulse test results in three different planes of an individual with ANSD. The head and eye velocities throughout different head impulses to the right or left side along with VOR gain and refixation saccades are shown.

In the figure 4.1.3.1, the presence of refixation saccades (covert, overt or covert + overt) in different canals as well as absence of it in few of them can be seen. Also figure

4.1.3.2 shows the presence of refixation saccades in none of the semi-circular canals measured in one of the normal hearing individuals.

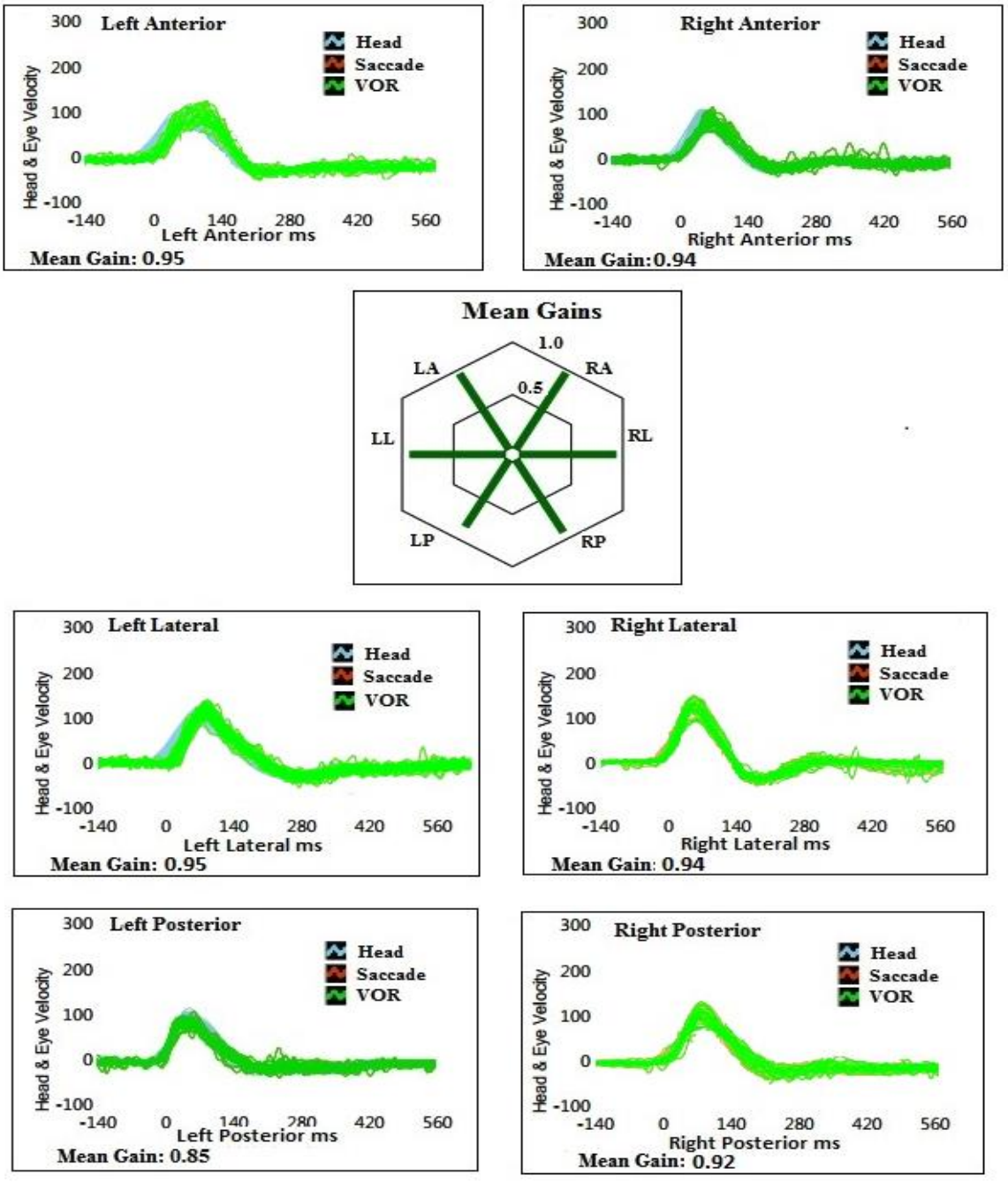


Figure 4.1.3.2: Video head-impulse test results in three different planes of a normal hearing individual with ANSD. The head and eye velocities throughout different head

impulses to the right or left side along with VOR gain and absence of refixation saccades are shown.

In the figure 4.1.3.2, the absence of any of the refixation saccades (covert, overt or covert + overt) in all six semi-circular canals can be seen.

4.2 Caloric test results in individuals with Auditory Neuropathy Spectrum Disorder

Bithermal caloric stimulation in all the normal hearing individuals participated in the study yielded cumulative frequencies for each of the four stimulations i.e. right cold (RC), left cold(LC), right warm(RW) and left warm(LW). The tracing of the nystagmus beats in one of the normal hearing individuals is given in figure 4.2.1.

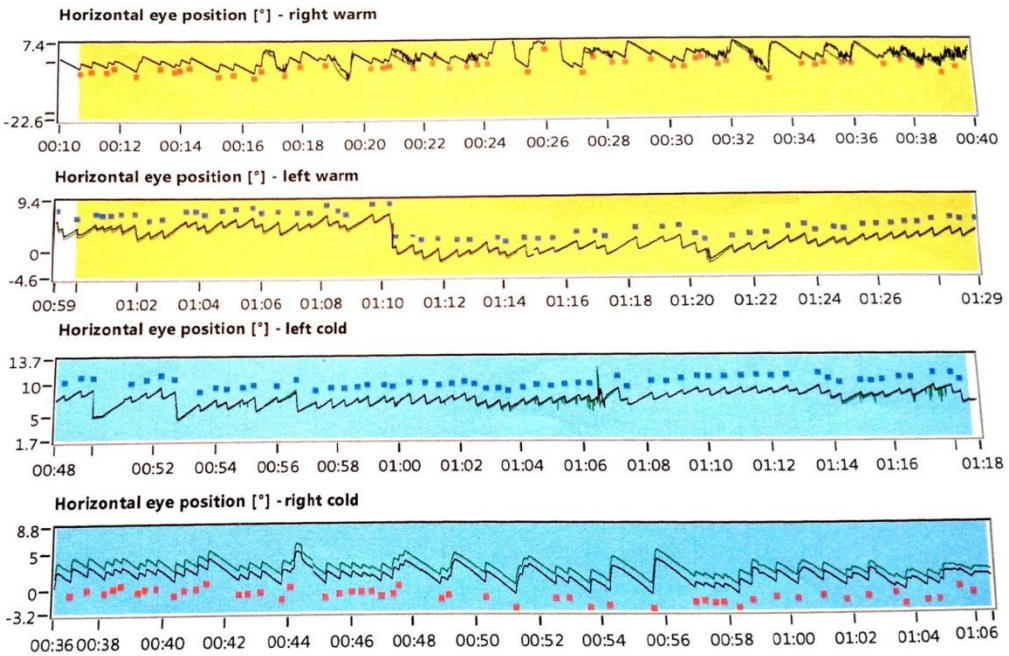


Figure 4.2.1: Tracing of a normal hearing individual obtained in caloric testing. Figure 4.2.1 shows the presence of nystagmus beats in all the four recordings.

It was found to have normal caloric response in all the normal hearing individuals based on the normative range of cumulative frequencies given in the table 4.2.1.

Table 4.2.1: Culmination frequency range (beats/30 seconds) for the bithermal caloric stimulation.

Stimulation temperature	Cumulative frequency (beats/ 30 sec)
Right warm	22-59
Right cold	22-63
Left warm	24-67
Left cold	27-68

Moreover the figure 4.2.2 represents Hail-Stoll butterfly chart with cumulation frequency of one of the normal hearing individual based on the number of nystagmus beats per 30 seconds in each of the 4 different stimulations.

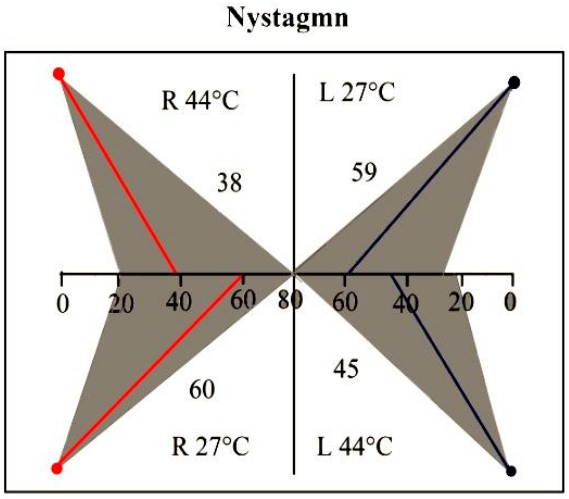


Figure 4.2.2: Hail-Stoll butterfly chart of one of the individuals with normal hearing.

The caloric test could be completed in ten participants with auditory neuropathy spectrum disorders due to various subject related problems. Four out of the five participants developed severe vertigo & vomiting sensation during the entire testing and the test was stopped for them, as these participants did not want to go ahead with the testing.

The tracing of the waveforms following the bithermal irrigation was recorded and analyzed to check for the presence of any nystagmus in each of the individuals with ANSD. The tracing of two of these individuals with and without nystagmus beats are shown in figures 4.2.3 and 4.2.4 respectively.

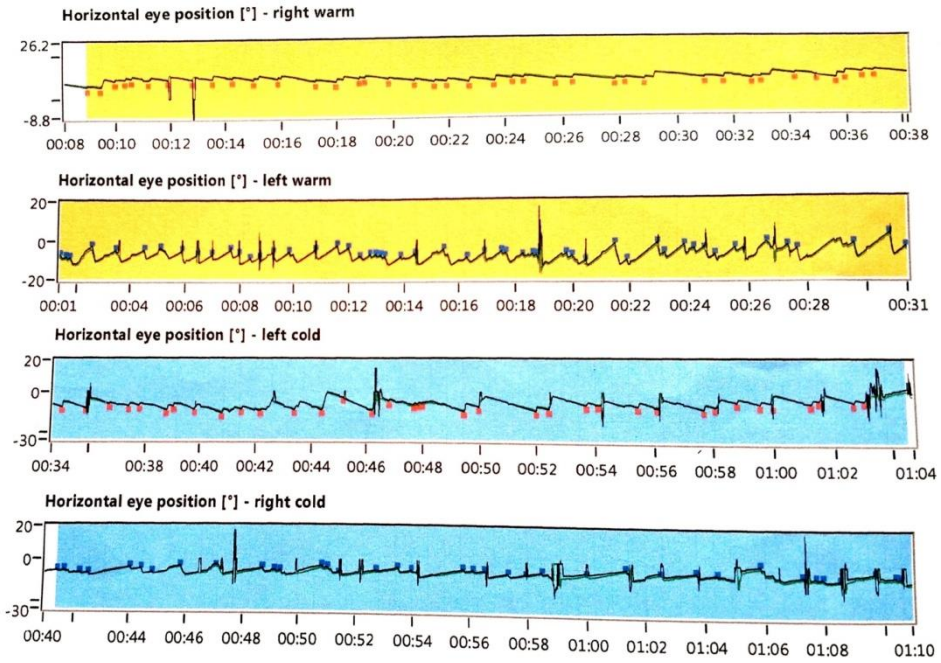


Figure 4.2.3: Tracing of an individual with ANSD in caloric testing. Figure 4.2.3 shows the presence of nystagmus beats in all the four recordings.

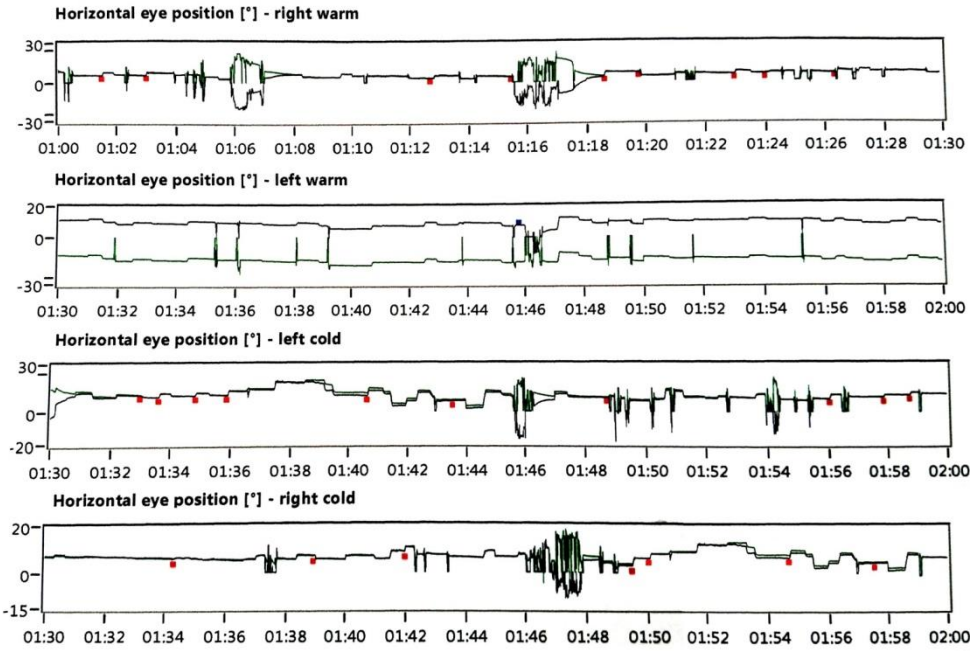
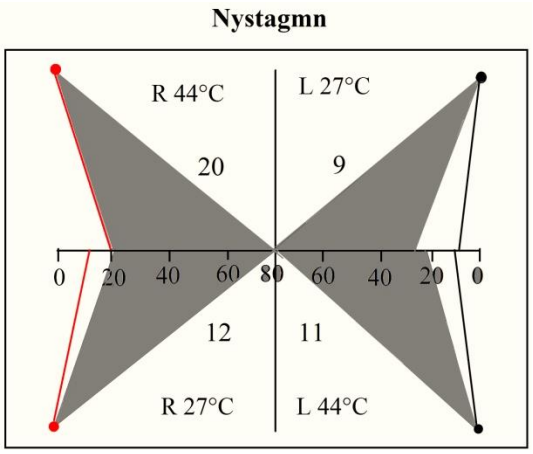


Figure 4.2.4: Tracing of an individual with ANSD in caloric testing. Figure 4.2.4 shows the absence of nystagmus beats in all the four recordings.

In most of the individuals with ANSD, there was prevalence of hypoactive response followed by few normal response. It was found to have 66.67% of hypoactive response for RW irrigation, 86.67% for LW irrigation, 86.67% for RC irrigation and 100% for LC irrigation in these individuals. Yet, three of them had normal cumulation frequency only in right warm (RW) caloric irrigation. However, none of the individuals had hyperactive response present.

These obtained results were plotted against the normative in Hail-Stoll butterfly chart. Hail-Stoll butterfly charts obtained for ten individuals with ANSD is represented in figure 4.2.5. Butterfly chart of five of the individuals couldn't be achieved due to technical difficulty.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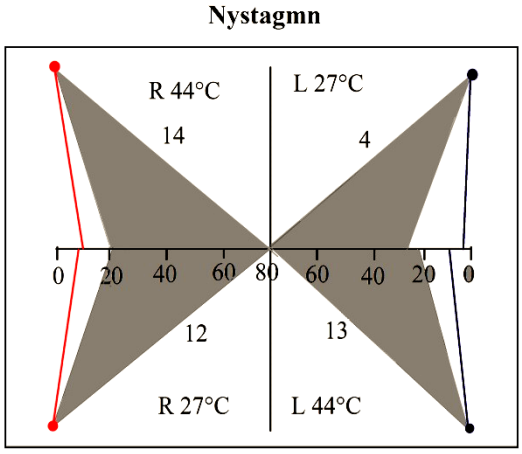
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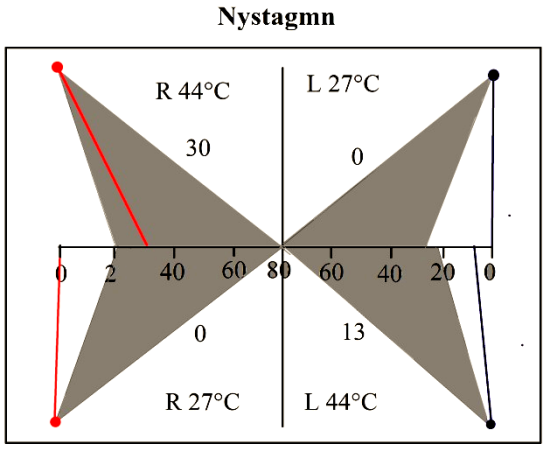
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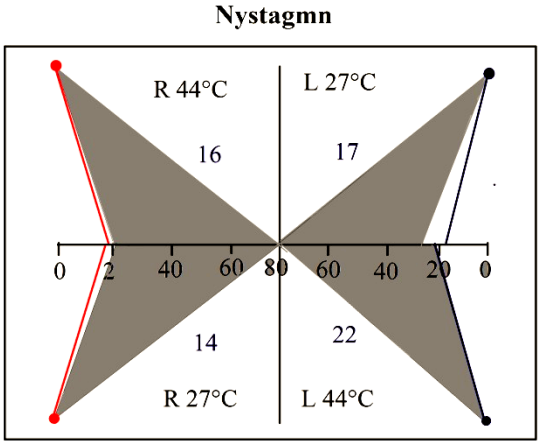
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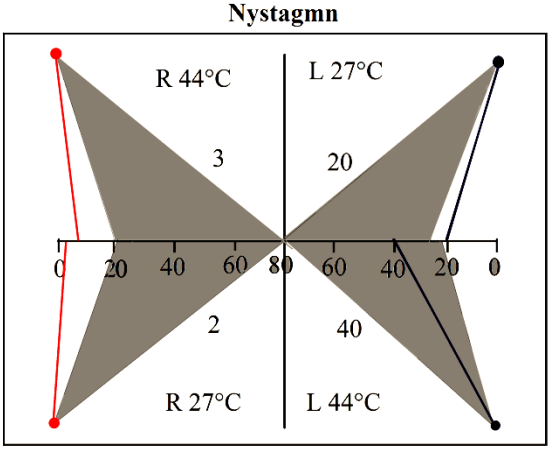
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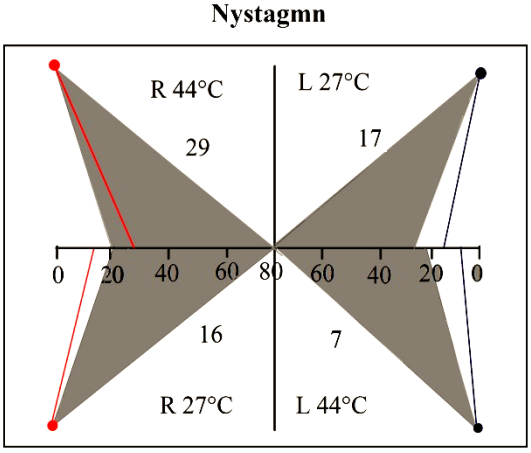
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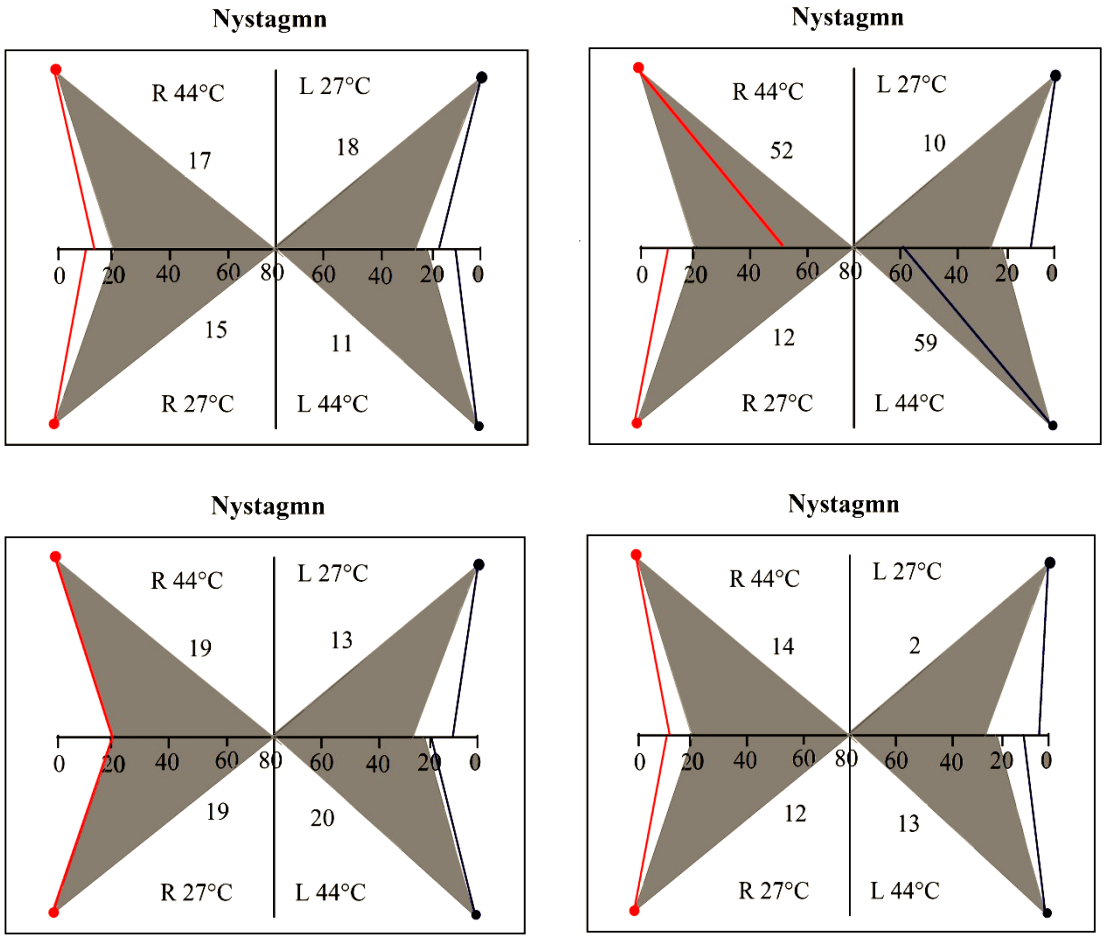

Figure 4.2.5: Hail-Stoll butterfly charts of 10 individuals with ANSD.

In the figure 4.2.5, Hail-Stoll butterfly chart of almost all the individuals with ANSD had cumulation frequency range lesser than that of lower limit of normative range for all four different caloric stimulations as given in the table 4.2.1.

4.3 Correlation of VOR gain and asymmetry with duration

Pearson's correlation was performed to understand the relation between the VOR gain and VOR gain asymmetry with the duration in individuals with ANSD. Tables 4.3.1 and 4.3.2 represent the correlation of VOR gain with duration and VOR gain asymmetry with duration in individuals with ANSD respectively.

Table 4.3.1: Correlation between VOR gain and duration of six semi-circular canals in individual with ANSD.

Semi-circular Canals	Duration
Left Lateral (LL)	0.64***
Right Lateral (RL)	0.16***
Left Anterior (LA)	0.48***
Right Anterior (RA)	0.06***
Left Posterior (LP)	0.08***
Right posterior (RP)	0.24***

Note: ***** -** r values with no significant correlation.

In the table 4.3.1 it can be seen that Pearson correlation between VOR gain of each canals and duration revealed no significant correlation.

Table 4.3.2: Correlation between VOR gain asymmetry and duration of six semi-circular canals in individual with ANSD.

VOR gain asymmetry	Duration
Lateral	0.05***
RALP	0.72***
LARP	0.31***

Note: ***** -** r values with no significant correlation.

Similarly, it can be seen in table 4.3.2 that there was no significant correlation between VOR gain asymmetry and duration for any of the three orthogonal planes.

4.4 Association of VOR gain with degree of hearing loss

Chi square test was administered to understand the association of VOR gain with the degree of hearing loss in specific ear in individuals with ANSD. Tables 4.4.1 and 4.4.2 represent the VOR gain and its association with the degree of hearing loss for right and left ear respectively.

Table 4.4.1: Association of VOR gain values with degree of hearing loss for right ear in individual with ANSD

Right Ear	**Right Lateral(RL)**		**Right Anterior(RA)**		**Right Posterior(RP)**	
Degree of Hearing loss	**Low gain**	**Normal gain**	**Low gain**	**Normal gain**	**Low gain**	**Normal gain**
Minimal	2	1	2	1	3	0
Moderate	5	2	5	2	5	2
Moderately severe	3	1	2	2	3	1
Severe	0	1	0	1	1	0
Total	10	5	9	6	12	3

Note: No significant association was seen between any of the canals and degree of hearing loss (Chi-square >0.05)

Table 4.4.1 shows the presence of variable VOR gain across degree of hearing loss in right ear. Also, in different degrees of hearing loss, there was low or normal VOR

gain. However, comparatively, most often it was seen to have low VOR gain across different degree of hearing loss.

Table 4.4.2: Association of VOR gain values with degree of hearing loss for left ear in individual with ANSD

Left Ear	Left Lateral(LL)		Left Anterior(LA)		Left Posterior(LP)	
Degree of Hearing loss	**Low gain**	**Normal gain**	**Low gain**	**Normal gain**	**Low gain**	**Normal gain**
Minimal	2	1	3	0	3	0
Moderate	5	3	7	1	8	0
Moderately severe	1	3	3	1	3	1
Severe	0	0	0	0	0	0
Total	8	7	13	2	14	1

Note: No significant association was seen between any of the canals and degree of hearing loss (Chi-square >0.05)

Similarly, table 4.4.2 shows the presence of variable VOR gain across degree of hearing loss in left ear. It was found to have low or normal VOR gain in different degrees of hearing loss. However, comparatively, most often it was seen to have low VOR gain across different degree of hearing loss. Also, none of the cases were reported to have severe hearing loss.

4.5 Association of caloric test result with degree of hearing loss

Chi square test was performed to understand the association of caloric test result and the degree of hearing loss in specific ear in individuals with ANSD. Tables 4.5.1 and

4.5.2 represent the caloric response and its association to the degree of hearing loss for right and left ear respectively.

Table 4.5.1: Association of caloric response with degree of hearing loss for right ear in individual with ANSD.

Right Ear	**Right Warm(RW)**		**Right Cold(RC)**	
Degree of hearing loss	**Normal**	**Hypoactive**	**Normal**	**Hypoactive**
Minimal	**2**	**1**		**3**
Moderate	**2**	**5**		**7**
Moderately severe	**1**	**3**		**4**
Severe	**0**	**1**		**1**
Total	**5**	**10**		**10**

Note: No significant association was seen in either of the bithermal stimulation and degree of hearing loss (Chi-square >0.05)

Table 4.5.1 shows the presence of variable caloric response across the degree of hearing loss in right ear. However, relatively, most often it was seen to have hypoactive caloric response across different degree of hearing loss. Also, in right cold stimulation, all the degree of hearing loss had hypoactive caloric response.

Table 4.5.2: Association of caloric response with degree of hearing loss for left ear in individual with ANSD

Left Ear	**Left Warm(LW)**		**Left Cold(LC)**	
Degree of hearing loss	**Normal**	**Hypoactive**	**Normal**	**Hypoactive**
Minimal	**1**	**2**	**1**	**2**

Moderate	**0**	**8**	**0**	**8**
Moderately severe	**1**	**3**	**1**	**3**
Severe	**0**	**0**	**0**	**0**
Total	**2**	**13**	**2**	**13**

Note: No significant association was seen between any of the bithermal stimulation and degree of hearing loss (Chi-square >0.05)

In left ear, caloric response was comparatively most often seen as hypoactive across different degree of hearing loss. In few of the individuals, it was observed to have normal response across different degree of hearing loss.

4.6 Association of caloric result with lateral canals VOR gain

Chi square test was administered to check the association of caloric test result with the VOR gain of lateral canals in specific ear in individuals with ANSD. Tables 4.6.1 and 4.6.2 represent the caloric response and its association to the VOR gain of lateral canals for right and left ear respectively.

Table 4.6.1: Association of caloric response with VOR gain of lateral canals for right ear in individual with ANSD

	Right Warm(RW)		**Right Cold(RC)**	
Right Lateral (RL)	**Normal**	**Hypoactive**	**Normal**	**Hypoactive**
Low Gain	3	7	0	10
Normal Gain	2	3	0	5
Total	5	10	0	15

Note: No significant association was seen between any of the bithermal stimulation and lateral canals (Chi-square >0.05)

Table 4.6.1 shows the presence of hypoactive caloric response most often in right warm (RW) stimulation in right lateral semi-circular canals with lower VOR gain. Moreover, in case of right cold (RC) stimulation, hypoactive response was present for all the individuals irrespective of the VOR gain. Also, for lower VOR gain of right lateral (RL), it was seen to have hypoactive response in right cold (RC) stimulation.

Table 4.6.2: Association of caloric response with VOR gain of lateral canals for left ear in individual with ANSD

Left Lateral (LL)	Left Warm(LW)		Left Cold(LC)	
	Normal	**Hypoactive**	**Normal**	**Hypoactive**
Low Gain	1	7	1	7
Normal Gain	1	6	1	6
Total	2	13	2	13

Note: No significant association was seen between any of the bithermal stimulation and lateral canals (Chi-square >0.05)

Table 4.6.2 shows the presence of hypoactive caloric response most often in both left warm (LW) and left cold (LC) stimulations irrespective of VOR gain in left lateral semi-circular canals. Also, it was observed to have more hypoactive response for lower VOR gain of left lateral (LL) comparatively.

To conclude, the vHIT findings revealed significantly reduced VOR gain values for all six semi-circular canals in individual with ANSD as compared to that of normal hearing individuals. Furthermore, VOR gain asymmetry was found to be significantly higher for all three orthogonal planes in the individuals with ANSD than the normal

hearing individuals. Also, all of these individuals had the corrective compensatory refixation saccades in at least one of the semi-circular canals which was found to be absent in normal hearing individuals. Moreover caloric test findings indicated the hypoactive response in most of the individuals with ANSD followed by few of them having normal response. However no significant correlation was found to be present between VOR gain and duration of disorder onset as well as VOR gain asymmetry and duration of disorder onset in individuals with ANSD. Neither VOR gain of all the canals nor bithermal caloric responses were found to be associated with degree of hearing loss in these individuals. Also, no association between the bithermal caloric response and VOR gain of lateral canals was found with respect to each ear.

Chapter 5

DISCUSSION

5.1. Video head impulse test

The recent technological advancement of vHIT as a non-invasive tool in the vestibular assessment was administered for the first time in understanding the physiological basis of semicircular canals of the individuals with ANSD.

5.1.1. VOR gain

In the present study, all normal hearing individuals had normal VOR gain values of >0.8. Most of these individuals had lower VOR gain of <0.8 except three of them. Thus the mean VOR gain values for all six semi-circular canals was significantly lower in individuals with ANSD than their normal hearing counterparts.

Similar reports of reduced VOR gain values as in individuals with ANSD, have been reported earlier in various peripheral vestibular disorders (H. G. Macdougall et al., 2013b; H. G. MacDougall et al., 2016; Weber et al., 2008). Most of these studies which have reported reduced VOR gain in different vestibular pathologies Blodow, Pannasch, and Walther (2013) reported abnormally reduced VOR gain values in 117 individuals with bilateral vestibulopathy. Another study by Blödow et al. (2014a) reported reduced VOR gain in 37% of 30 individuals with Meniere's disease. Taylor et al. (2016) reported 43 individuals with bilateral vestibular neuritis where the reduced VOR gain was observed in 97.7% horizontal canals, 90.7% in anterior canals and 39.5% in canals. Thus, it can be concluded that in various vestibular pathologies, irrespective of the site of

lesion(whether the pathology is restricted in inner ear or pathology is confined to vestibular nerve) there is an abnormal reduced gain.

Conversely few studies have reported VOR gain as less efficient parameter in assessing vestibular loss. Study by Korsager, Wanscher, Schmidt, and Faber (2016) did vHIT study in 25 cochlear implantee. vHIT was performed by two different examiners on each of the patients where it revealed the occurrence of saccades more reliable than varying VOR gain values. Also another study on vHIT in 30 individuals with motion sickness reported the significant difference in VOR gain values only in RALP plane than the control group. However saccades was found to be higher in the motion sickness group (Neupane et al, 2017).

However in the present study, the reduced VOR gain in individuals with ANSD indicates the probability of peripheral vestibular nerve involvement such that the functioning of its innervated end organ is also affected (S. K. Sinha, A. Barman, N. K. Singh, G. Rajeshwari, & R. Sharanya, 2013). Anatomical study by Arnold Starr et al. (2003) on peripheral vestibular nerve in individuals with auditory neuropathy has revealed reduced quantity of vestibular nerve fibers as well as Scarpa ganglion cells. Also the fragmented myelinated layer as large as the diameter of the nerve fibers, thinning of the myelin sheath of the remaining axons, incomplete remyelination and distorted peripheral vestibular nerve can explain its inability to coordinate the innervated end organs function appropriately. Hence these structural bases of peripheral vestibular nerve in individuals with ANSD results in reduced neural input as well as impaired synchronous firing of the vestibular nerve resulting in the presence of reduced VOR gain in these individuals.

In the present study, 3 of the individuals with ANSD had normal VOR gain which could be due to the bilateral distribution and slower development of the neuropathic degeneration (Kaushlendra Kumar, Sinha, Singh, Bharti, & Barman, 2007). Also, the diameter of the vestibular nerve is more than the auditory nerve, hence even if both the cochlear and vestibular nerves are equally affected, the action potentials transmission would be affected more in case of cochlear nerve than that of its vestibular counterpart. Hence the evident manifestation and development of auditory deficits in ANSD would be more than the vestibular manifestation which could provide more chances for compensation in vestibular symptoms resulting normal VOR gain values in these 3 individuals with ANSD.

5.1.2 VOR gain asymmetry

In the present study, the individuals with ANSD had significantly higher VOR gain asymmetry in all three coplanar axis (Lateral, LARP and RALP) than their normal hearing counterparts.

Similar finding has been reported by Neupane et al (2017) in individuals with motion sickness where it was explained to have occurred due to the intra-sensory conflict between the semicircular canals of same planes. This phenomenon in return would have given rise to the discrepancy in neural input from three orthogonal planes to the cortical balance areas. Such a dilemmatic circumstances could generate difficulty in understanding the precise postural alignment of the body even when whole body is stimulated with similar acceleration.

However, except one study, none of the other studies have yet been published reporting VOR gain asymmetry in any of the vestibular pathologies. This is the primary study reporting significantly higher VOR gain asymmetry in individuals with ANSD However, before considering VOR gain asymmetry as a vital parameter in detecting vestibular pathology, there is a need of evaluating the sensitivity of VOR gain asymmetry across various different clinical vestibular conditions.

5.1.3 Refixation saccades

In the present study, all normal hearing individuals had absent corrective refixation saccade. However, it was present in 100% of individuals with ANSD.

The existence of these refixation saccades have also been reported earlier in various vestibular related pathologies (Jiménez & Fernández, 2016; H. G. Macdougall et al., 2013b; H. G. MacDougall et al., 2009; Redondo-Martinez et al., 2016). Blodow et al. (2013) reported the presence of compensatory refixation saccades as an outcome for VOR gain reduction in individuals with vestibulopathy. Similar findings were reported by Neupane et al (2017) in individuals with motion sickness and indicated the presence of compensatory refixation saccades as a good parameter in assessing these individuals.

Refixation saccades are suggestive of impaired semicircular canals such that its unable to retain the gaze stability with movement of eye in equal velocity and opposite direction to that of the head rotation(Weber et al., 2008). These occur when the variation is present between the stimulated sides of the coplanar canals to that of the non-stimulated side therefore, making VOR generate compensatory eye movement to maintain gaze stability even during head rotation (Bronstein & Gresty, 1991). Refixation

saccades are of very high velocity that can result in degradation of an image in retina, thus suppressing the vision during its onset and time of occurrence (Matin, 1974). However, this suppressing characteristic of saccades helps in elimination of those retinal image which are smeared due to inadequate slow phase eye velocity that can be seen in most of the vestibular pathology (Hamish Gavin MacDougall & Curthoys, 2012).

Therefore, in the present study, considering the presence of refixation saccades in individuals with ANSD, it is clear that these individuals with vestibular loss have difficulty in maintaining gaze on the target. Thus, these saccades help in image stability but not with slow compensatory eye movement. It's the ballistic high velocity eye movement of these refixation saccades that eliminates smeared image at retina due to inadequate VOR resulting in visual stimulus free of smearing. Therefore the presence of refixation saccades can be taken as an indication of vestibular loss individuals with ANSD.

5.2 Caloric test

In the present study, for right warm stimulation 66.67% of the participants with ANSD had hypoactive responses, 86.67% had hypoactive responses for left warm irrigation, 86.67% had hypoactive responses for left warm and 100% of the participants had hypoactive responses for left cold irrigation.

Such an response with significant absence of any quantifiable nystagmus beats has been reported as an indicative factor for the presence of predominant peripheral vestibular pathology (Biswas, 2009). Similar findings have been reported earlier as the absence of any quantifiable nystagmus in caloric test in 2 individuals with ANSD (Kaga

et al., 1996). In another study by Abdel-Nasser et al. (2006) reported 44% of individuals with ANSD with absence of response for bithermal caloric irrigation suggesting the presence of bilateral peripheral vestibular pathology. Similarly, Kaga (2009) studied on 5 individuals with ANSD where ice water caloric irrigation was done in both the ears. However no noticeable nystagmus beats as the responses were observed suggesting the authors to classify them as 'auditory-vestibular neuropathy'. Author reported the condition as the probable involvement of superior vestibular nerve or/and its innervated end organ. In other three individuals with ANSD, it was found to have normal results in vestibular evaluations suggesting it to be 'auditory neuropathy only'. Moreover many studies have indicated the involvement of vestibular nerve along with auditory nerve in individuals with auditory nerve in individuals with auditory neuropathy spectrum disorders based on the caloric tests (Abdel-Nasser et al., 2006; Sheykholeslami et al., 2000; S. K. Sinha, A. Barman, et al., 2013; Von Brevern et al., 1997). Moreover none of the central tests of vestibular test battery revealed any positive results suggesting the existence of peripheral pathology within superior vestibular nerve and its innervated end organ..

The hypoactive responses obtained in the present study could be due to the abnormality of the vestibular nerves found in individuals with auditory neuropathy spectrum disorders. Arnold Starr et al. (2003) reported structural changes at the level of vestibular nerve in those individuals in comparison to the normal control group. Also, the reduced number of vestibular nerve fibers joining receptor organ and Scarpa ganglion was observed. Moreover both the auditory and vestibular nerve was found to have a beaded distorted appearance in the individuals with ANSD. In addition, the myelin layer

was found to have fragmentations with larger gaps than the diameter of the nerve fiber itself. Such damage to vestibular nerve fibers would lead to impairment of the action potentials conduction along these fibers and hence, the caloric test will show an absence of responses.

5.3 Correlation of VOR gain and asymmetry with duration

There was found to be no correlation between VOR gain and asymmetry with duration of disorder in individuals with ANSD.

None of the earlier studies have reported the correlation of VOR gain and asymmetry with duration of disorder. In auditory domain, Jijo and Yathiraj (2012) reported no significant correlation between degree of hearing loss and speech identification scores with the duration of the disorder in individuals with ANSD. There were group of individuals with ANSD having similar degree of hearing loss and speech identification scores even though the duration of the disorder was variable and vice versa (Jijo & Yathiraj, 2012; Arnold Starr et al., 1996). In individuals with auditory neuropathy, Spoendlin (1974) also reported the presence of individualistic variability in the range of characteristic features of the disorder even if the pathophysiology is similar. Hence this highlights the heterogeneity of the disorder and its nature that varies across each individuals with auditory neuropathy spectrum disorders.

Therefore considering the unique variations in audiological functioning of individuals with ANSD in spite of having same or different duration of the disorder, one can presume it to be similar in case of vestibular functioning of these individuals. Hence, the individualistic variations may be present across each subject despite of the duration of

disorder resulting in no correlation of the VOR gain and asymmetry with duration of disorder.

5.4 Association of VOR gain and caloric response with degree of hearing loss

There was found to be no association between VOR gain and caloric response with degree of hearing loss in individuals with ANSD.

Similar result was reported by Sujeet et al. (2014) where they found dissociation between the caloric response and cVEMP response with degree of hearing loss. Even in auditory domain, the studies have been reported of the dissociation between degree of hearing loss and speech recognition scores (Jijo & Yathiraj, 2012; Zeng, 2000).

In the present study, the lack of dissociation between the vestibular responses and degree of hearing loss could be due to the fact that these are the functions performed by two different systems (auditory and vestibular systems) in different manner. Here the auditory system is responsible for the acoustic signals whereas peripheral vestibular system is responsible for head movements and balance. Therefore, the processing of these functions at the level of auditory nerve or vestibular nerve may go differently, resulting in lack of association between the VOR gain and caloric response with degree of hearing loss.

5.5 Association of caloric result with lateral canals VOR gain

There was found to be dissociation between VOR gain of the lateral canals and canal paresis as indicated by bithermal caloric test in the individuals with ANSD.

Mickael Bartolomeo et al. (2014) reported significantly consistent association between VOR gain and canal paresis in individuals with vestibular neuritis. However the range of canal paresis values reported in the study was high i.e. more than 50% which suggested the notion that the VOR gain response is sensitive to larger canal paresis values and not to the smaller ones which are still considered clinically significant.

Therefore, in the present study, considering dissociation between hVOR gain and canal paresis values in the individuals with ANSD, it is suggestive that the results may be the outcome of the variation in stimulus as well as response parameters between the two tests. The major differences between the vHIT and caloric test are the temporal frequency of the stimulus used in each test (vHIT with high frequency stimulus vs caloric with low frequency stimulus) as well as the stimulus delivery mode (vHIT with head jerks vs caloric with thermal gradient) (McCaslin et al., 2014).

Moreover the disagreement in hVOR gain and canal paresis values in the individuals with ANSD may be anatomically described based on the neurophysiology of the crista which are found to have both peripheral and central zones (Eatock & Songer, 2011). Afferent fibres from the peripheral zone of crista that synapse mainly with Type II hair cells, have slow conduction velocities retaining regular tonic neural spike timing and have higher gain at low frequencies with small phase shifts. However, afferent fibres from the central zone of crista that synapse mainly with Type I hair cells have irregular firing rates and have higher gain at high frequencies with large phase leads (Goldberg, 1991; Haque, Angelaki, & Dickman, 2004). Therefore, it can be presumed that a short duration head jerk in vHIT may stimulate the irregular fibres on the central zone of crista and tonic caloric stimulation may stimulate the regular fibres on the peripheral zone of

crista. Thus its presently accepted that there can be selective weakening of different zones of crista that code low and high frequency movements of head or any other body parts (Park, Migliaccio, Della Santina, Minor, & Carey, 2005). Therefore, dissociated test result of hVOR gain and caloric values in the individuals with ANSD may be due to the variation in functioning of the semi-circular canals for different frequency domains in these individuals and the variation in the range of impairment in the afferent fibres of two different zones in individual with ANSD.

To conclude, the present study revealed the reduced VOR gain in individuals with ANSD which could be due to the peripheral vestibular nerve involvement such that the functioning of its innervated end organ is also affected resulting in higher VOR gain asymmetry in these individuals. The compensatory refixation saccades in individuals with ANSD is suggestive of the presence of vestibular loss that could have given rise to the difficulty in maintaining gaze on the target. Also the hypoactive response for caloric test reveals the condition as the probable involvement of superior vestibular nerve or/and its innervated end organ in individuals with ANSD. However, the lack of correlation between VOR gain and asymmetry with the duration of disorder highlights the heterogeneity of the disorder and its nature that may vary across each individuals. Also, no association of VOR gain and caloric response with degree of hearing loss in individuals with ANSD suggests the processing variations of these functions at the level of auditory nerve or vestibular nerve. Moreover, the lack of association between VOR gain of the lateral canals and canal paresis in the individuals with ANSD indicates the variation in stimulus as well as response parameters between the two tests.

Chapter 6

SUMMARY AND CONCLUSIONS

Most of the existing literature regarding the etiology, symptomatology, clinical features and results on ANSD is confined within the cochlear branch of 8th cranial nerve. However, even if it's intrinsically linked with the common pathway, the neuropathy of the vestibular branch is rarely mentioned in the literature. As the superior and inferior vestibular nerves supply neural impulse to otoliths and semi-circular canals, it's likely that even the neuropathic conditions do affect their physiology (Akdogan et al., 2008). However the rare description of vestibular neuropathy could be due to the slow progressive development of the pathology, likely, not much expressed due to the effective vestibular compensatory mechanism, and more consideration given on proprioception and cerebellar functioning for the imbalance problem in individual with ANSD (Melgaard & Zilstorff, 1979). Thus, even being prevalent, vestibular examinations are not done routinely in individuals with ANSD.

In the present study to understand the correlation between vHIT and caloric test in individuals with ANSD, 30 subjects were taken for the study which included two groups.

1. Group I comprised of 15 individuals, 7 males and 8 females, n= 30 ears with the age range of 17 to 38 years (mean age= 25.2yrs) with ANSD.
2. Group II comprised of 15 individuals, 10 males and 5 females in the age range of 18 to 24years (mean = 22.1yrs) with normal hearing sensitivity.

All the participants underwent detailed audiological test battery and vestibular tests. The vestibular tests comprised of the vHIT and caloric test. The test responses were analyzed as:

1. In vHIT, VOR gain, VOR gain asymmetry and refixation saccades were measured.
2. In caloric test, the cumulative frequency for bithermal stimulation was analyzed and plotted in Hail-Stoll Butterfly chart.

These measured data were analyzed statistically analyzed so as to better understand the findings.

1. Descriptive statistics was performed to find out the mean and standard deviation of VOR gain and VOR gain asymmetry in normal hearing individuals and individuals with ANSD.
2. Descriptive analysis of refixation saccades in each of the canals in individuals with ANSD was measured.
3. Descriptive analysis of bithermal caloric response in individuals with ANSD.
4. Pearson's correlation to find the correlation between VOR gain and asymmetry with duration of disorder.
5. Chi-square test to find association between VOR gain and the degree of hearing loss in individuals with ANSD.
6. Chi-square test to find association between caloric response and the degree of hearing loss in individuals with ANSD.
7. Chi-square test to find association between caloric response and lateral canals VOR gain.

The results of the study revealed that

1) All normal hearing individuals had normal VOR gain values of >0.8. Moreover, vHIT was used for the first time in analyzing the functioning of semi-circular canals of the individuals with ANSD. Most of these individuals had lower VOR gain of <0.8 except three of them. Thus, it was found that the mean VOR gain values for all six semi-circular canals was significantly lower in individuals with ANSD than their normal hearing counterparts.
2) The individuals with ANSD had significantly higher VOR gain asymmetry in all three coplanar axis (Lateral, LARP and RALP) than their normal hearing counterparts.
3) All normal hearing individuals had absent corrective refixation saccade. However, it was present in 100% of individuals with ANSD in one or the other planes. Both covert as well as overt saccades were present in individuals with auditory neuropathy spectrum disorders.
4) Caloric test yielded the most prevalent response as hypoactive in 66.67% for RW irrigation, 86.67% for LW irrigation, 86.67% for RC irrigation and 100% for LC irrigation. None of the individuals had hyperactive response present.
5) There was found to be no correlation between VOR gain and asymmetry with duration of disorder in individuals with ANSD.
6) There was found to be no association of VOR gain and caloric response with degree of hearing loss in individuals with ANSD.
7) There was found to be dissociation between VOR gain of the lateral canals and canal paresis as indicated by bithermal caloric test in the individuals with ANSD.

Conclusion

Hence the findings of the present study suggest majority of individuals with ANSD to have vestibular dysfunctions in both the tests. However, the lack of positive correlation between the vHIT and caloric test results in these individuals suggests the ability of two tests in assessing two different frequency domains of the same semi-circular canal. Also as vHIT assesses all six semicircular canals, it can be taken as the complementary test in vestibular test battery approach to further diagnose individuals with ANSD to have 'auditory neuropathy only' or 'auditory-vestibular neuropathy' as recommended by Kaga (2009). Thus, the individuals with auditory neuropathy shall be assessed for vestibular dysfunction. If any of the individuals with auditory neuropathy spectrum disorder shows any vestibular sign and symptoms appropriate rehabilitation programme must start. Also, combination of various vestibular test will help us understand the difference between peripheral and central vestibular lesion to help us formulate the better rehabilitation programme.

Implications of the study

- The study gives us an idea about the functioning of the vestibular system in individuals with ANSD.
- The study throws light on mechanisms of VOR reflex in individual with ANSD from the normal individuals.
- The study helps in understanding the compensation phenomenon (in occurs) in individual with ANSD.

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