VESTIBULAR EVOKED MYOGENIC POTENTIALS AND VIDEO HEAD IMPULSE TEST IN AUDITORY NEUROPATHY SPECTRUM DISORDER

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May, 2017

CERTIFICATE

This is to certify that this dissertation entitled **"Vestibular evoked myogenic potentials and video head impulse test in auditory neuropathy spectrum disorder"** is a bonafide work submitted in part fulfillment for degree of Master of Science (Audiology) of the student Registration Number: 15AUD006. This has been carried out under the guidance of faculty of the institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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CERTIFICATE

This is to certify that this dissertation entitled **"Vestibular evoked myogenic potentials and video head impulse test in auditory neuropathy spectrum disorder"** has been prepared under my supervision and guidance. It is also being certified that this dissertation has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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DECLARATION

This is to certify that this dissertation entitled **"Vestibular evoked myogenic potentials and video head impulse test in auditory neuropathy spectrum disorder"** is the result of my own study under the guidance of **Dr.Niraj Kumar Singh,** Lecturer in Audiology, Department of Audiology, All India Institute of Speech and Hearing, Mysore, and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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Abstract

Several studies have reported a possible vestibular nerve involvement along with the cochlear nerve in auditory neuropathy spectrum disorder (ANSD). However, assessment of entire vestibular nerve originating from all five vestibular end organs has never been reported previously. Therefore, present study aimed at evaluating the responses of fibres originating from both otolith organs and all three semicircular canals in individuals with ANSD. A total of 20 individuals with ANSD and 20 healthy individuals within the age range of 11-40 years underwent behavioural balance assessment, cVEMP, oVEMP and vHIT. Significantly more number of individuals demonstrated abnormal findings on Fukuda stepping test, both classical and sharpened Romberg tests and tandem gait test than healthy individuals ($p < 0.05$). No significant group difference existed on cerebellar test ($p > 0.05$). The response rates were significantly lower and latencies of cVEMP and oVEMP significantly longer in individuals with ANSD than healthy individuals ($p < 0.05$). While cVEMP amplitude was significantly smaller in individuals with ANSD than healthy individuals ($p < 0.05$), there was no group difference in oVEMP amplitude ($p > 0.05$). Reduced VOR gain and refixation saccades were present in larger proportion of individuals with ANSD than healthy individuals ($p < 0.05$). Finally, findings of oVEMP were significantly correlated with vHIT findings for lateral and anterior canals ($p < 0.05$). No significant correlation was seen between findings of cVEMP and vHIT for any semicircular canal.

Key words: *ANSD, behavioural balance test, cVEMP, oVEMP, vHIT*

"In the name of God, the Most Gracious, the Most Merciful"

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CHAPTER 1

INTRODUCTION

Auditory neuropathy spectrum disorder (ANSD) is a consensus terminology that describes a type of hearing loss characterized by abnormal auditory nerve function although cochlear hair cell function is largely unaffected, especially the outer hair cells' (OHCs) activity (Batuk, Sennaroglu, Yucel, Cinar, & Sennaroglu, 2015). The audiological findings have revealed affected or mostly disproportionate speech identification scores for the degree of hearing loss (Abdala, Sininger, & Starr, 2000; Zeng, Oba, Garde, Sininger, & Starr, 2001), present oto-acoustic emissions (Rance, Beer, Cone- Wesson, Shepherd, Dowell, King, Rickards, & Clark, 1999), absent acoustic reflexes (Sininger & Oba, 2001) and absent or abnormal auditory brainstem responses (Starr, Picton, Sininger, Hood, & Berlin, 1996; Rance et al., 1999; Sininger & Oba, 2001). All these together produce profound effects on an individual's life by breaking down the communication link with the significant others in the family and the rest of the society.

As with the variability in the symptoms and severity, the prevalence of ANSD has been reported to be variable across age groups and in different parts of the world. Among children in general population, the prevalence was found to vary from 0.027% to 0.044% (Kirkim, Serbetcioglu, Erdag, & Ceryan, 2008; Dowley, Whitehouse, Mason, Cope, Grant, & Gibbin, 2009). Among those with sensorineural hearing loss, the prevalence was reported to vary from 0.005% to 15.38% (Rance et al., 1999; Madden, Rutter, Hilbert, Greinwald, & Choo, 2002; Tang, McPherson, Yuen, Wong, & Lee, 2004; Kumar & Jayaram, 2006; Dowley et al., 2009).

The cochlear and the vestibular branches together form the vestibulocochlear nerve and it is this anatomic relationship that lead several scientists to believe that an abnormal cochlear nerve function might also be associated with abnormality in the vestibular nerve function. This paved the way for investigations searching for abnormalities in the vestibular branch of the VIIIth cranial nerve in individuals with ANSD. The speculations were confirmed as facts by the findings of abnormal vestibular function in a proportion of these individuals (Sheykholeslami, Kaga, Murofushi, & Hughes, 2000). Subsequently, the studies using bithermal caloric test, cVEMP and oVEMP have shown vestibular dysfunction in a large contingent of individuals with ANSD (Fujikawa & Starr, 2000; Wu & Young, 2004; Sheykholeslami, Schmerber, Kermany, & Kaga, 2005; Kumar, Sinha, Singh, Bharati, & Barman, 2007; Akdogan, Selcuk, Ozcan, & Dere, 2008; Sazgar, Yazdani, Rezazadeh, & Yazdi, 2010; Sinha, Shankar, & Sharanya,2013; Ismail, Makkey, Besher, & Galhom, 2014).

All the above tests used to study vestibular function in individuals with ANSD have largely concentrated on assessing the inferior vestibular nerve function or superior nerve function for the fibers arising out of lateral semicircular canal, utricle or saccule. There are no studies on functioning of the fibers arising from the two vertical canals. A recent addition to the vestibular test battery is video head impulse test (vHIT), which can assess each of the 6 semicircular canals separately.

Until 1988, the functional assessment of vertical canals was limited to only the ears with BPPV. With advent of vHIT, along with its improvisations for the vertical canal pairs (Aw, Haslwanter, Halmagyi, Curthoys, Yavor, & Todd, 1996; Halmagyi & Curthoys, 1999), the functional assessment of these canals and their pathways was possible. vHIT makes use of small yet high velocity head jerks for eliciting vestibulo-

ocular reflex (VOR) in the respective canal planes. The VOR gain and presence of refixation saccades are the parameters used to draw inferences about the functioning of the semicircular canals and their pathways to the ocular muscles.

Need for the study

ANSD is one of the most widely researched area in the field of audiology. Considering the anatomical relevance of the vestibular and cochlear branches, the studies exploring vestibular function have also been conducted. While most of these studies have reported abnormal inferior vestibular nerve function in individuals with ANSD by virtue of observing absent or abnormal cervical VEMP (Kumar et al., 2007; Sazgar et al., 2010), a few have reported abnormal superior vestibular nerve function through results of electronystagmography (Fujikawa & Starr, 2000; Sheykholeslami et al., 2005) or videonystagmography (Ismail et al., 2014). Ocular vestibular evoked myogenic potentials are the least explored among the popular tests of vestibular assessment and the findings of the studies showed completely absent (Sinha et al., 2013) or abnormally reduced amplitudes and prolonged latencies of oVEMPs (Singh, Sinha, & Barman, 2016) in individuals with ANSD. Nonetheless, the results of oVEMP in individuals with ANSD appear to indicate towards presence of deficiently functioning superior vestibular nerve that carries the signals along the utriculo-ocular pathway.

Although the above studies independently reported about various components of the vestibular nerve, a holistic view about the integrity of the vestibular structures and an explicit knowledge about which part of the vestibular system is affected cannot be concluded from them when the tests like VEMPs, caloric or manoeuvres are carried out solely. The manoeuvres cannot help in cases with ANSD as there are no free floating otoconia crystals in the semicircular canals. VEMPs can only assess for

the functioning of the otolith mediated pathways whereas bithermal caloric test can provide information regarding the fibres originating in the lateral semicircular canals. Further, the studies have shown dissociation between the caloric and vHIT outcomes in some vestibular pathologies (McCaslin, Rivas, Jacobson, & Bennett, 2014; McGarvie, Curthoys, MacDougall, & Halmagyi, 2015; Redondo-Martinez, Becares-Martinez, Orts- Alborch, Garcia- Callejo, Perez- Carbonell, & Marco- Algarra, 2016) and therefore even the caloric results may not completely be able to explain the superior nerve function in individuals with ANSD. Therefore, a combination of VEMPs and vHIT could be used to determine the overall integrity of the vestibular system in individuals with ANSD. However, such a study has not been reported so far, to the best of our knowledge.

Aim of the study

The present study aimed to assess the functioning of saccule, utricle, and all three semicircular canals using cVEMP, oVEMP, and vHIT respectively in individuals with ANSD.

Objectives

In order to fulfill the above aim, the following objectives were explored:

1. To describe the findings of behavioral tests, cVEMP, oVEMP and vHIT in individuals with ANSD and healthy individuals
2. To compare the response rate, amplitude and latency related parameters of cVEMP between healthy individuals and individuals with ANSD.
3. To compare the response rate, amplitude and latency related parameters of oVEMP between healthy individuals and individuals with ANSD.

4. To compare the VOR gain originating from the three semicircular canals between participants with ANSD and participants with healthy audio-vestibular system.
5. To compare the refixation saccades for head movements in the planes of the three semicircular canals between participants with ANSD and participants with healthy audio-vestibular system.
6. To examine the correlation between VOR gain of vHIT and peak to peak amplitude of cVEMP and oVEMP.

CHAPTER 2

REVIEW OF LITERATURE

Normal cochlear amplifier function and abnormal auditory nerve function are the characteristic features of the hearing problem known as auditory neuropathy spectrum disorders (ANSD) (Starr et al., 1996; Berlin, Hood, & Rose, 2001). The key audiological findings in individuals with ANSD are affected or mostly disproportionate speech identification scores for the degree of hearing loss, present oto-acoustic emissions, absent acoustic reflexes and absent or abnormal auditory brainstem responses.

The physiological mechanisms involved in the abnormal function in the auditory system resulting in ANSD are varied. The post-synaptic disorder involves the number and functions of auditory nerves and is referred to as Type I auditory neuropathy (Type I AN) and the pre-synaptic disorder affecting inner hair cells ability to synthesize or release neurotransmitters is referred to as Type II AN.As ANSD is a systemic disease and as vestibulocochlear nerve comprises of the cochlear and the vestibular branches, an abnormal cochlear nerve function might be associated with abnormality in the vestibular nerve function. Research have confirmed abnormal vestibular nerve function in these individuals (Fujikawa & Starr, 2000; Sheykholeslami et al., 2000; Wu & Young, 2004; Sheykholeslami et al., 2005; Kumar et al., 2007; Akdogan et al., 2008; Sazgar et al., 2010; Sinha et al., 2013; Ismail et al., 2014).

Behavioural assessment in ANSD

In a study by Sheykholeslami et al., 2000, three subjects who were identified as having auditory neuropathy were taken. Vestibular analyses including Romberg,

Mann and stepping tests. Abnormal results were obtained in eyes closed condition and spontaneous nystagmus was not found in them. They concluded that in patients with isolated auditory neuropathy, the auditory system as well as the vestibular system may be affected and suggested the use of the term cochlear neuropathy to characterize those patients with involvement of only the auditory branch of the VIIIth cranial nerve.

Sinha et al (2011) reported the findings of Romberg and Fukuda stepping test in 3 subjects diagnosed as having auditory neuropathy. Two subjects had deviations to the right while one subject performed the test normally. The conclusions made were abnormality of the vestibular nerve, both superior and inferior, and also the subclinical manifestation of the vestibular neuropathy which were attributed to the compensatory changes that occur over time.

Caloric test in ANSD

In a study by Starr et al (1996), 10 patients with auditory neuropathy were subjected to caloric testing and the results revealed 3 patients to have horizontal nystagmus on lateral gaze, 2 had absent responses whereas 5 were asymptomatic. The authors suggested the abnormal vestibular results to be a part of a generalized neuropathic disorder affecting both the auditory and vestibular components of the VIIIth cranial nerve.

Three subjects with ANSD were subjected to ice water caloric stimulation in a study done by Sheykholeslami et al (2000). One subject presented with horizontal nystagmus without vertigo in the right ear alone and in the other 2 subjects there were no responses bilaterally. The study concluded that vestibular branch and its innervated structures can also be affected along with the auditory branch of the eighth cranial

nerve in individuals with ANSD. Similar results were reported in several other studies (Fujikawa & Starr, 2000; Starr, Michalewski, Zeng, Fujikawa- Brooks, Linthicum, Kim, Winnier, & Keats, 2003; Abdel-Nasser, Elkhayat, Khalil & Mahmoud, 2006; Sinha et al., 2011).

In a study by Sheykholeslami et al in 2005 a contradictory results were found. In the study, a 21-year-old female with isolated ANSD was subjected to caloric stimulation and the results were normal which revealed that in patients with ANSD who do not present with peripheral neuropathy, a range of variability is also demonstrated.

Cervical vestibular evoked myogenic potential in ANSD

The integrity of saccule and sacculocollic pathway can be assessed using cervical vestibular evoked myogenic potential (cVEMP). In a study by Sheykholeslami et al., 2000 where on 3 subjects identified as having auditory neuropathy, cVEMP for 500 Hz air conducted tone stimuli was performed. cVEMP responses were absent in all the subjects. Involvement of the inferior vestibular nerve in cases with auditory neuropathy were concluded from the study.

In a study by Kumar et al (2007), 20 ears of individuals with auditory neuropathy were assessed. Of them, 16 ears had abnormal or affected cVEMP responses. Several other studies have also reported similar findings of cVEMP in cases of ANSD (Sazgar et al., 2010; Singh et al., 2015). Abnormal inferior vestibular nerve function in individuals with ANSD can be inferred from these studies.

Ocular vestibular evoked myogenic potential in ANSD

Ocular vestibular evoked myogenic potentials (oVEMP) have been less often been investigated in individuals with ANSD than cVEMP. In a study by Sinha et al., 2013, subjected 11 participants with ANSD to oVEMPs. They observed complete absence of oVEMP in all 11 individuals. It was concluded that there is an involvement of the superior vestibular nerve along with the cochlear branch of the VIIIth nerve in individuals with ANSD.

In a study by Singh et al (2016), 31 individuals with ANSD underwent oVEMP. Only 6 ears had presence of oVEMP out of the 62. Abnormally reduced amplitudes and prolonged latencies of oVEMPs were in these 6 ears. The presence of responses in them was attributed the heterogeneity in the ANSD profile. The results of oVEMP in individuals with ANSD indicate the deficiently functioning superior vestibular nerve that carries the signals along the utriculo-ocular pathway.

Video head impulse test in ANSD

Most of the studies were concentrated on assessing the inferior vestibular nerve function or superior nerve function for the fibers arising out of lateral semicircular canal and utricle. Video head impulse test (vHIT) can be used to assess each of the semicircular canals separately. There are no studies on functioning of the fibers arising from the two vertical canals.

CHAPTER 3

METHOD

Participants

A total of 20 individuals diagnosed with ANSD in the age range of 11-40 years served as participants for the study. Participants with middle ear pathology, hypertension and diabetes were excluded. The study also excluded individuals having well known vestibular pathologies like Meniere's disease, benign paroxysmal positional vertigo, labyrinthitis, vestibular neuritis, vestibular schwannoma and multiple sclerosis. This was ensured through detailed structured case history and evaluations by otolaryngologist and neurologist. The degree of hearing loss and speech identification abilities were not constraints for participant selection, as degree of hearing loss has no significant impact on the outcomes of VEMP (Kalaiah, Kumar, & Ranjan, 2014) and vHIT, as it (that is, vHIT) does not rely on use of acoustic stimuli. Another set of 20 participants with healthy audio-vestibular system served as the comparison group. Normal auditory system was ensured through pure-tone average (PTA) ≤ 15 dBHL, 'A' type tympnogram with presence of acoustic reflexes at 100 dBHL (both ipsilateral and contralateral) and presence of OAEs. Normal vestibular system function was ensured using behavioural vestibular assessment. Behavioural balance assessment tests included Fukuda stepping test (deviation < 45^{o}, lateral shift <1m), Romberg test (no swaying), sharpened Romberg test (no swaying), finger-to-nose-test (no undershoot, overshoot or tremors), diadokinetic test performed with alternate supination and pronation of palm (no repetitive movements), tracking shin bone with heels (no tremors) and tandem gait test (maintain a straight line without losing balance).

Test environment and instrumentation

All the tests were carried out in an acoustically and electrically shielded room where the ambient noise levels were within the permissible limits as per ANSI standards (ANSI S3.1-1991). A calibrated two-channel diagnostic audiometer Grason-Stadler Incorporated 61 (GSI-61) with TDH 39 supra-aural headphones and Radioear B-71 bone vibrator was used for pure-tone and speech audiometry. GSI tympstar was used for the assessment of middle ear status and ILO-V6 oto-acoustic emission equipment was used for obtaining transient evoked oto-acoustic emission (TEOAE) for fulfilment of the subject selection criteria. Biologic Navigator Pro evoked potential system with impedance matched SINSER insert ear phones was used for recording ABR as well as cervical and ocular vestibular evoked myogenic potentials. ICS impulse, a commercially available video head impulse system, was used for assessing the functionality of the vestibulo-ocular reflex pathway originating from the three semicircular canals using its various modules namely 'Lateral', LARP and RALP (in 'RALP' and 'LARP', the alphabet 'L' stands for left side, 'R' for right side, 'A' for anterior semicircular canal & 'P' for posterior semicircular canal).

Procedure

In order to ensure the fulfilment of participant selection criteria, detailed case history was followed by pure-tone audiometry, speech audiometry, immittance evaluation, otoacoustic emissions and auditory brainstem response recordings. Subsequently, the participants underwent behavioural balance assessment tests, cVEMP, oVEMP and vHIT.

Behavioural balance assessment.

The balance assessment included Fukuda test, Romberg test, sharpened Romberg test, finger-to-nose-test, diadokinetic test (alternate supination and pronation of palm), tracking shin bone with heels and tandem gait test. In Fukuda stepping test, the participants were asked to march inside a circle of 1 meter diameter while keeping their hands outstretched in front (parallel to the ground and to each other) and the angle of deviation and the distance moved were noted. An angle $>45^{o}$ and displacement >1 meter was considered as abnormal result (Harit & Singh, 2012). In Romberg test, the participants were asked to stand erect with their feet together and their hands outstretched in front (same hand position to Fukuda stepping test). The test was administered in eyes open and closed condition. The movement of the body was observed and a positive sign for balance impairment was considered when there was swaying or toppling over. Similar responses were looked for when the participant was asked to stand heel-to-toe for sharpened Romberg test (hand position was same as that of the Romberg test). In finger-to-nose-test, the participants had to touch their nose tip and the finger tip of the clinician alternately and undershoot/overshoot of the target or presence of essential tremors was considered abnormal. Diadokinetic test was done by instructing the participants to place their palm in prone and supine positions alternately and rapidly. Supination ends with the palm facing up and pronation ends with the palm facing down and observation for uncoordinated or repetitive movements were considered as abnormal finding on this test. In tracking shin bone with heel, the task was to track from knee to ankle along the shin bone using heel of the other foot and uncoordinated or clumsy movements were deemed abnormal. In tandem gait test, the participant was instructed to walk heel-to-toe along an imaginary straight line on the floor. Inability to follow a straight path or frequent

imbalance (rising of hand to counter against tilt of body in one direction to avoid loss of balance) was taken as an abnormal result.

Cervical VEMP.

The participants were seated on a comfortable chair. Non-inverting, inverting and ground electrodes were placed on the sternocleidomastoid muscle at a point 2/3rd of its way up, the sternoclavicular junction and lower forehead, respectively. Absolute and inter-electrode impedance were maintained below 5 kΩ and 2 kΩ, respectively. Rarefaction polarity tone-bursts of 500 Hz were delivered at 125 dB peSPL to the ear using a repetition rate of 5.1/s. Participants were instructed to turn their head to the side opposite to the ear in which the acoustic stimuli were presented. This posture ensured stiffening (tensing) of the sternocleidomastoid muscle. In order to ensure against the effects of variability in muscle activation, 'pre-stimulus rectify' protocol, which corrects for EMG during recording, of Biologic Navigator Pro evoked potential system was used. The responses were filtered between 10 to 1500 Hz and recorded using an epoch of 74 ms (64 ms post-stimulus & 10 ms pre-stimulus baseline) for 200 sweeps. The averaged response was amplified by a factor of 5000. Peaks P1 and N1 were marked by an experienced audiologist.

Ocular VEMP.

Maintaining the same sitting position, as that during cVEMP recording, the participants underwent oVEMP recording. Non-inverting, inverting and ground electrodes were placed 1 cm below the lower eyelid, 2 cm below the non-inverting electrode and on the lower forehead, respectively. Inter-electrode impedance was maintained below 2 kΩ whereas absolute electrode impedances were ensured below 5 kΩ. Rarefaction polarity tone-bursts of 500 Hz were presented at a rate of 5.1/s

monaurally at an intensity of 125 dB peSPL to the ear contralateral to the eyes below which electrodes were placed. Participants were instructed to maintain gaze in superomedial plane, fixated at about 30^{o}. The responses were filtered between 0.1 Hz and 1000 Hz and recorded using an epoch of 74 ms (64 ms post-stimulus and 10 ms pre-stimulus). The responses were averaged over 200 stimuli and multiplied by a factor of 30,000. The peaks n1 and p1 were identified by an experienced audiologist.

Video head impulse test.

Participants were asked to sit in an upright position and were made to wear a pair of goggles mounted with a monocular camera and a transparent mirror coated with a metallic film (half-silvered mirror) that allowed reflection of the eye back to the camera and also allowed the participant being tested to look through them. Head movements were measured by a sensor (accelerometer) within the goggles. Testing was preceded by a calibration procedure in which the participant was instructed to track two laser dots that appeared on the wall alternately at an angle of 10^{o} on either side of the mid-point. Following the calibration procedure, the clinician instructed the participant to gaze at a target dot on the wall about 1 m in front of him/her at eye level, and gave the participant brief and abrupt head impulses randomly. The head rotations were made with a head velocity of 100^{o}/s to 250^{o}/s through a small angle (about 10-20^{o}) and 20 impulses were recorded on each side specific to each plane (lateral / LARP / RALP). The swift movement of the eye was captured by the high speed fire wire camera and software was used to process it. At the end of each head impulse, the ratio of head and eye velocity provided the VOR gain. A mean gain value was obtained for 20 impulse recordings for each side in each plane. Presence of refixation saccades was also noted and considered abnormal only when a minimum of

50% traces corresponding to any particular direction of head impulses contained overt or covert saccades.

Statistical analyses

Shapiro-Wilk's test of normality was administered to decide upon the use of parametric / non-parametric statistical procedures. Results revealed non-normal distribution of data ($p < 0.05$). Therefore non-parametric statistical analyses procedures were used. Equality of test for proportions was used for comparison of proportion of individuals with abnormal results between the groups. Mann-Whitney *U* test was done for between group comparison of latencies and amplitude of cVEMP and oVEMP and VOR gain of vHIT. Spearman's correlation analysis was done for investigating the relationship between VOR gain of vHIT and amplitudes of cVEMP and oVEMP. In addition, descriptive statistics were also performed to obtain mean, standard deviation and median. All the statistical analyses were performed using statistical package for social sciences (SPSS) version 17.0, except equality of test for proportions which was done using Smith's statistical package, a free public domain software.

CHAPTER 4

RESULTS

The aim of the study was to assess the functioning of saccule, utricle, and all 6 semicircular canals in individuals with ANSD and compare them to those in the individuals with healthy auditory and vestibular systems. To achieve the aim, behavioural balance assessment, cVEMP, oVEMP and vHIT were administered on all the 40 participants (20 with ANSD & remaining 20 with no audio-vestibular dysfunction) in the present study.

Behavioural tests in individuals with ANSD

Present study had 20 individuals with ANSD. All of them underwent behavioural balance assessment tests. The tests administered were Fukuda stepping test, Romberg test, sharpened Romberg test, tandem gait test, finger-to-nose-test (past pointing test), diadokinetic test (alternate supination and pronation of palm) and tracking shin bone with heel. All the tests were carried out as described in the 'Method' section of the present study. A large contingent of these participants (55% or more on various tests) demonstrated abnormal results on Fukuda stepping test, both classical and sharpened Romberg tests and tandem gait test. Relatively fewer participants showed abnormal results on the remaining behavioural tests (maximum 25% cerebellar tests that tests for muscle coordination). Table 1 shows the results of each of these tests in individuals with ANSD.

Table 1.

Number and percentage of individuals with normal and abnormal results and outcomes of equality of test for proportions for between groups comparison on behavioural balance assessment tests between healthy individuals and individuals with ANSD

Name of the test	Individuals with ANSD		Healthy individuals		Equality of test for proportions	
	Abnormal results (N)	Abnormal results (in %)	Abnormal results (N)	Abnormal results (in %)	Z-value	*p*-value
Fukuda stepping test	15	75	02	10	**4.15**	**0.00003**
Romberg test	11	55	02	10	**3.03**	**0.002**
Sharpened Romberg test	14	70	02	10	**3.87**	**0.00003**
Tandem gait test	15	75	02	10	**4.15**	**0.0001**
Finger-to-nose test	05	25	00	00	**2.39**	**0.016**
Diadokinetic test	03	15	00	00	1.80	0.071
Tracking shin by heel	04	20	00	00	**2.10**	**0.035**

Note: 'N'- number of individuals with abnormal result; Bold faced fonts indicate statistically significant difference ($p< 0.05$).

Behavioural tests in healthy individuals

A total of 20 individuals underwent behavioural balance assessment. Abnormal results were observed in only 2 (10%) of these individuals on Fukuda stepping test, both classical and sharpened Romberg tests and tandem gait test. The remaining tests had all healthy individuals showing normal results. The outcomes of behavioural balance assessment are shown in Table 1.

Comparison of behavioural balance assessment between healthy individuals and individuals with ANSD

All participants with ANSD as well as the healthy individuals underwent behavioural balance assessment. Equality of test for proportions was performed to compare the proportion of individuals with abnormal results on each of the behavioural tests between the groups. The results revealed abnormal results in significantly higher proportion of individuals with ANSD than the comparison group (healthy individuals) on all the tests ($p < 0.05$), but one (diadokinetic test). The outcomes of equality of test for proportions of each of the behavioural tests (Z- & p-values) are given in Table 1.

cVEMP in individuals with ANSD

All 20 individuals with ANSD underwent ipsilateral recording of cVEMP from both their ears. Figure 1 shows cVEMP waveforms obtained from a representative participant in the ANSD group.

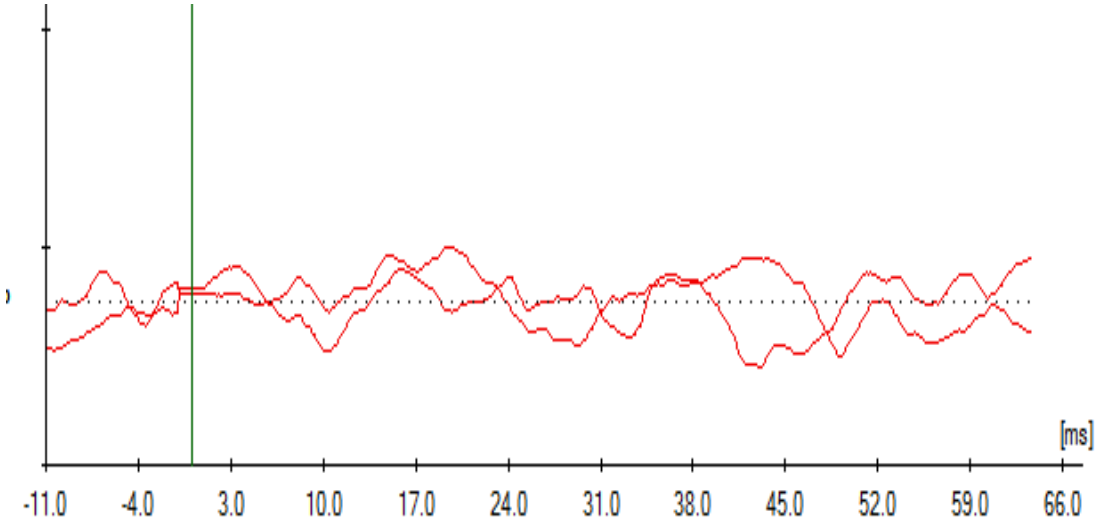

Figure 1: Representative cVEMP waveforms obtained from an individual with ANSD.

Replicable cVEMPs were present in 9 ears (4 left & 5 right ears; 4 individuals bilaterally & 1 individual unilaterally). This amounted to 22.50% response rate of cVEMP in case of ANSD. Table 2 shows response rate and mean, standard deviation and median of latencies and peak-to-peak amplitude of cVEMP in individuals with ANSD.

Table 2.

Response rates and median of latencies and peak-to-peak amplitude of cVEMP and oVEMP in healthy individuals and individuals with ANSD

	cVEMP								oVEMP							
Group	N	RR (%)	Latency (in ms)				Peak-to-peak amplitude (in µV)		N	RR (%)	Latency (in ms)				Peak-to-peak amplitude (in µV)	
			P1		N1						n1		p1			
			Mean (SD)	Med	Mean (SD)	Med	Mean (SD)	Med			Mean (SD)	Med	Mean (SD)	Med	Mean (SD)	Med
ANSD	09	22.50	18.08 (3.85)	16.99	22.69 (3.74)	23.18	17.93 (11.74)	13.31	07	17.50	18.05 (2.83)	19.31	22.45 (3.30)	23.54	2.81 (1.27)	2.53
Healthy individuals	40	100	15.49 (1.17)	15.67	20.75 (1.81)	20.56	33.63 (18.35)	29.45	40	100	11.99 (0.80)	12.10	16.62 (0.90)	16.76	3.32 (1.65)	2.86

Note: 'N'- number of ears with presence of response; 'RR'- response rate; 'cVEMP'- cervical vestibular evoked myogenic potentials; 'oVEMP'- ocular vestibular evoked myogenic potentials; 'P1'- first positive peak of cVEMP; 'N1'- first negative peak of cVEMP; 'n1'- first negative peak of oVEMP; 'p1'- first positive peak of oVEMP; 'SD'- standard deviation; 'Med'- median.

cVEMP in healthy individuals

All 20 healthy individuals underwent ipsilateral cVEMP recording from both their ears. Figure 2 shows cVEMP waveforms obtained from a healthy individual.

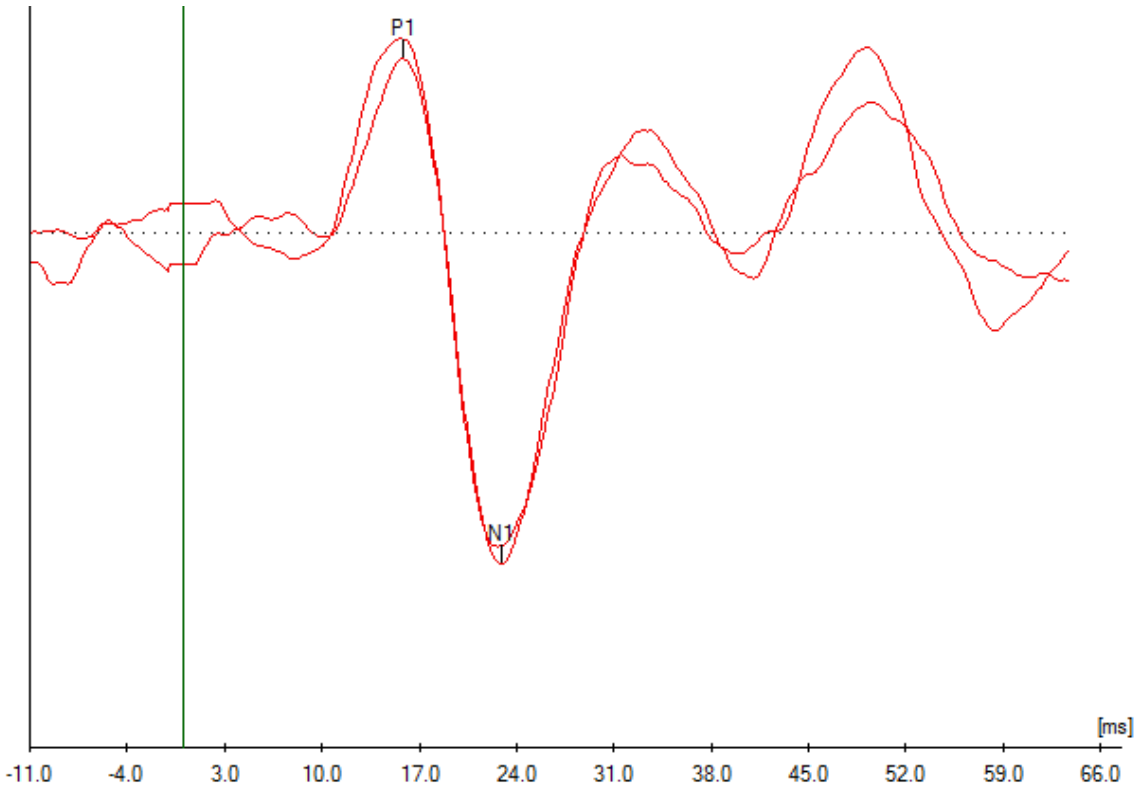

Figure 2: Representative cVEMP waveforms obtained from a healthy individual.

All 20 healthy individuals demonstrated replicable cVEMP waveforms with a positive and a negative peak in both ears. Therefore the response rate was 100%. Latencies of P1 and N1 peaks and peak to peak amplitude were obtained from the waveforms and subjected to descriptive statistics to find mean, standard deviation and median of these parameters. Table 2 shows the outcomes of descriptive statistics for cVEMP in healthy individuals.

Comparison of cVEMP between healthy individuals and individuals with ANSD

Equality of test for proportions was done to compare the response rate between healthy individuals and individuals with ANSD. The results revealed significantly lower response rate in the ANSD group than the group of individuals with ANSD [Z = 6.92, $p < 0.001$]. Further, latencies and peak-to-peak amplitudes were compared between the groups using separate Mann-Whitney *U* test for each of these parameters. The results revealed significantly shorter P1 latency [Z = -2.39, $p < 0.05$], and smaller peak-to-peak amplitude [Z = -2.96, $p < 0.01$] in the ANSD group than the comparison group comprising of healthy individuals. However, there was no significant difference in N1 latency between the groups [Z = -1.43, $p > 0.5$]. Figure 3 shows the mean and 95% confidence intervals of latencies and peak-to-peak amplitude of cVEMP and the outcomes of Mann-Whitney *U* test for between groups comparison.

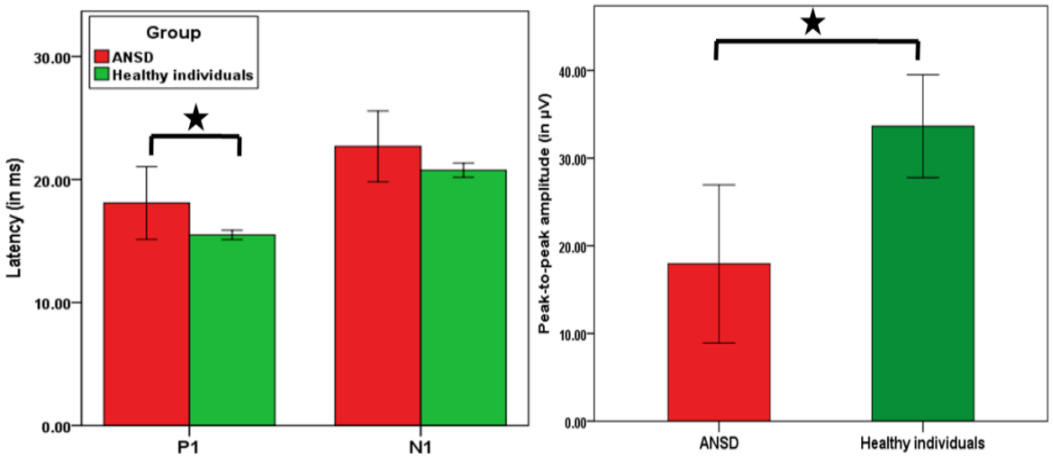

Figure 3: Mean and 95% confidence intervals of latencies (left panel) and peak-to-peak amplitude (right panel) of cVEMP in healthy individuals and individuals with ANSD and the outcomes of Mann-Whitney *U* test for between groups comparison. Star-marked comparisons represent statistically significant difference between the groups ($p < 0.05$).

oVEMP in individuals with ANSD

All 20 individuals with ANSD underwent contralateral recording of oVEMP from both their ears. Figure 4 shows oVEMP waveforms obtained from a representative participant in the ANSD group.

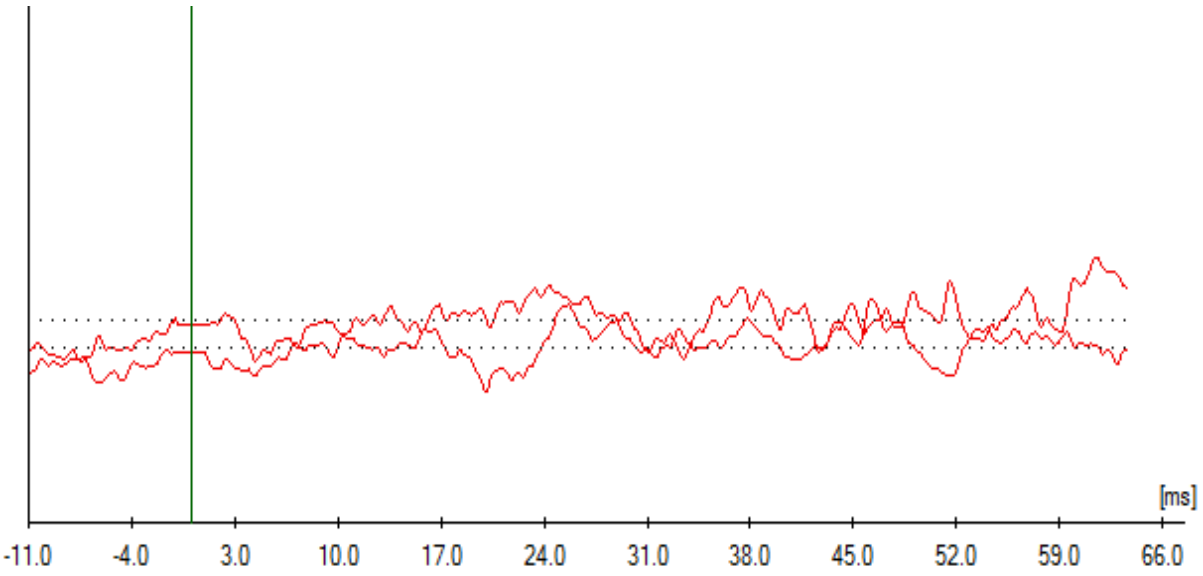

Figure 4: Representative oVEMP obtained from an individual with ANSD.

Replicable oVEMPs were present in 7 ears (3 left & 4 right ears; 3 individuals bilaterally & 1 individual unilaterally). This amounted to 17.50% response rate of oVEMP in case of ANSD. Descriptive statistics was done to obtain mean, standard deviation and median latencies and amplitude of oVEMP in individuals with ANSD who had presence of oVEMP responses. Table 2 shows response rate and mean, standard deviation and median of latencies and peak-to-peak amplitude of oVEMP in individuals with ANSD.

oVEMP in healthy individuals

All 20 healthy individuals underwent contralateral oVEMP recording from both their ears. Figure 5 shows oVEMP waveforms obtained from a healthy individual.

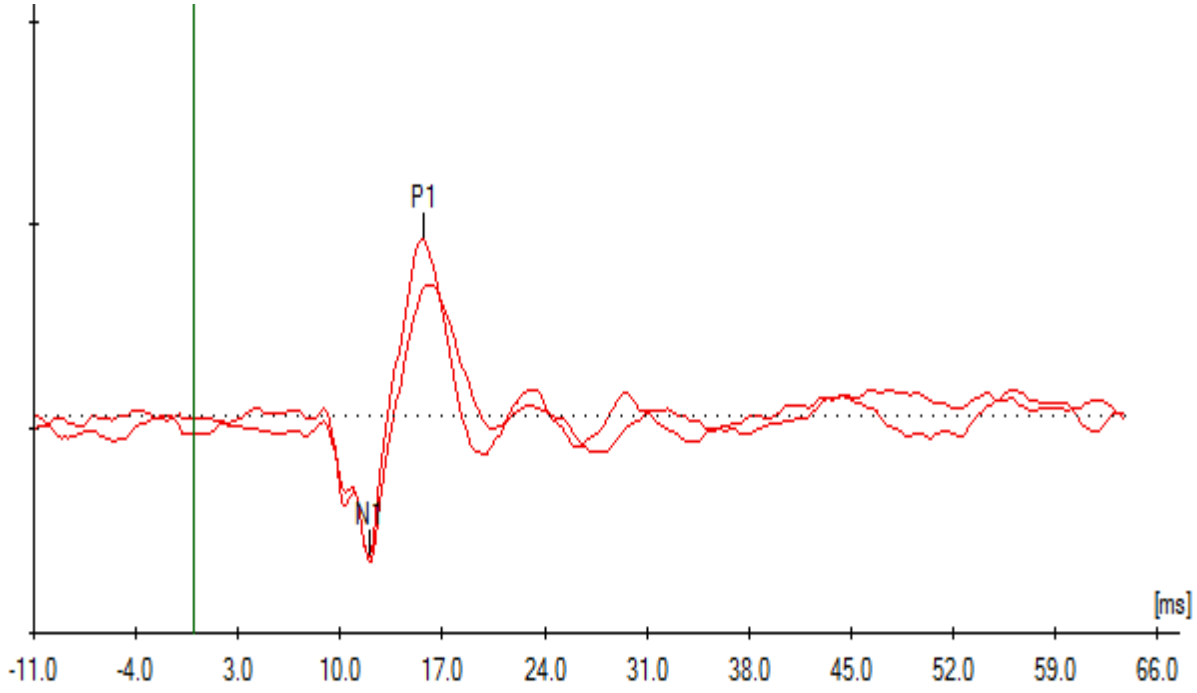

Figure 5: Representative oVEMP waveforms obtained from a healthy individual.

All 20 healthy individuals demonstrated replicable oVEMP waveforms with a negative peak and a positive in both ears. Therefore the response rate was 100%. Latencies of n1 and p1 peaks and peak to peak amplitude were obtained from the waveforms and subjected to descriptive statistics to find mean, standard deviation and median of these parameters. Table 2 shows the outcomes of descriptive statistics for oVEMP in healthy individuals.

Comparison of oVEMP between healthy individuals and individuals with ANSD

Equality of test for proportions for comparison of response rates between the groups revealed significantly lower response rates in ANSD group compared to the healthy individuals [Z = 7.49, $p < 0.001$]. Further, comparison of latencies and peak-to-peak amplitude between the groups was done using separate Mann-Whitney *U* tests for each parameter. Results revealed significantly longer n1 [Z = -3.92, $p < 0.001$] and p1 [Z = -3.41, $p < 0.01$] latencies of oVEMP in the ANSD group than healthy individuals. However, there was no group difference in peak-to-peak amplitude [Z = -0.39, $p > 0.05$]. Figure 6 shows mean and 95% confidence intervals of latencies and peak-to-peak amplitude of oVEMP in both groups and the outcomes of Mann-Whitney *U* test for between group comparisons.

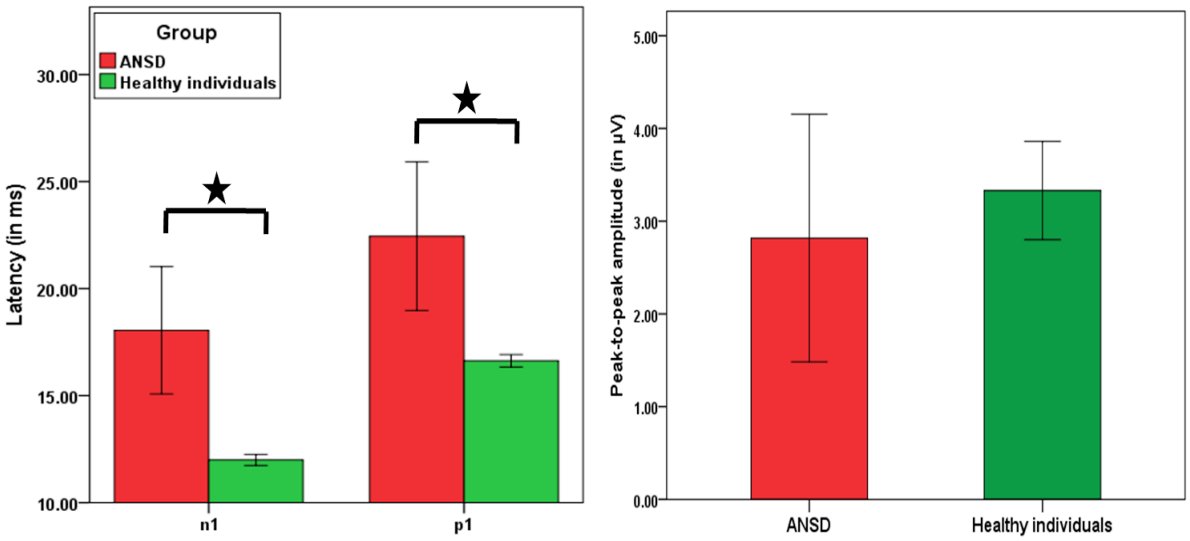

Figure 6: Mean and 95% confidence intervals of latencies (left panel) and peak-to-peak amplitude of oVEMP in healthy individuals and individuals with ANSD and the outcomes of Mann-Whitney *U* test for between group comparisons. Star-marked comparisons are statistically significant ($p < 0.01$).

vHIT in individuals with ANSD

Video head impulse test was administered by using head impulses along the planes of all six semicircular canals. Figure 7 shows head and eye velocity waveforms for all six semicircular canals and VOR gains obtained for them from an individual with ANSD.

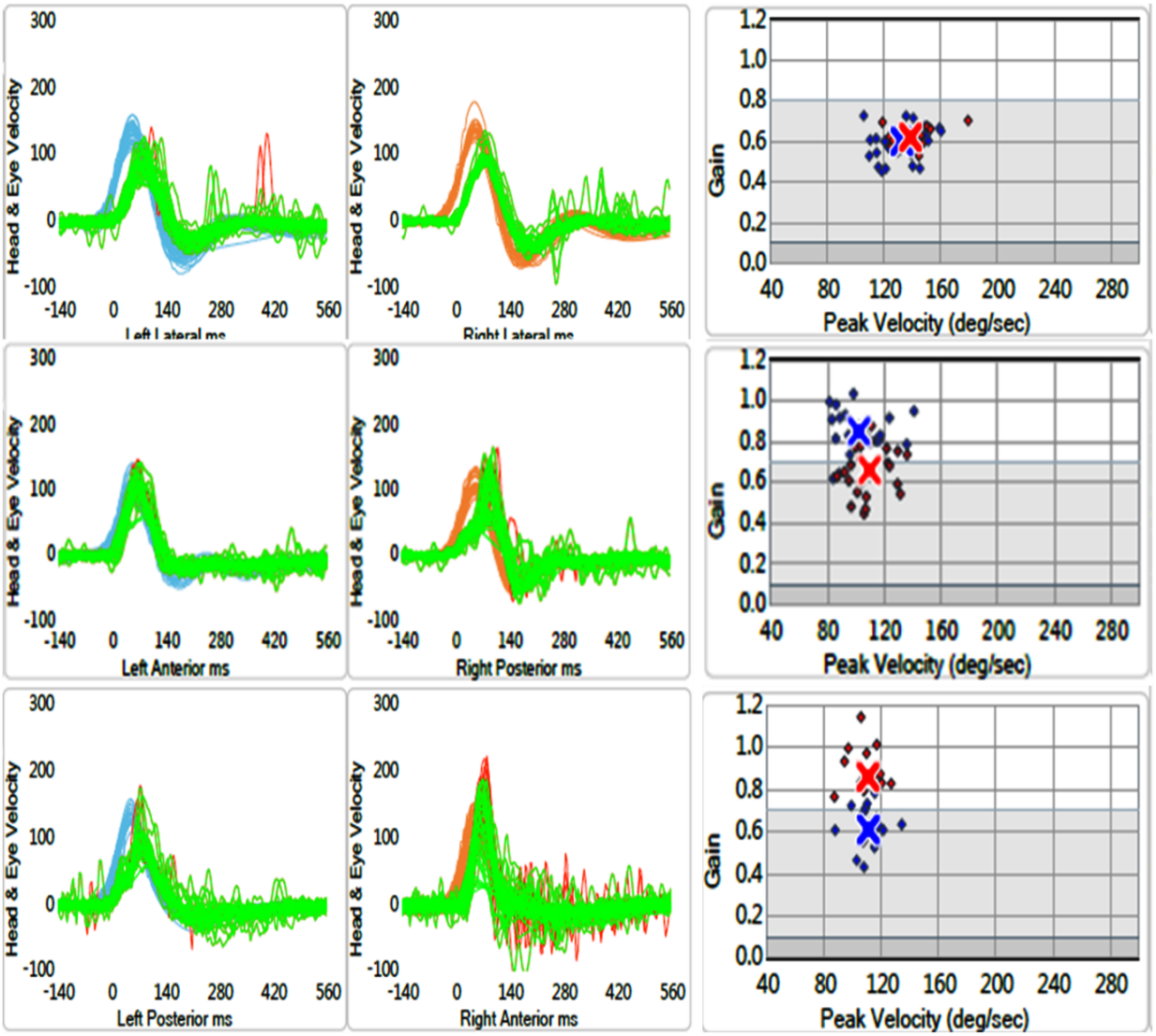

Figure 7: Head velocities, eye velocities and VOR gain for lateral (top panel), RALP (bottom panel) and LARP (intermediate panel) modules obtained from an individual with ANSD.

Parameters evaluated were presence of refixation saccades and VOR gain. Refixation saccades were considered to be present when overt or covert saccades were present on more than 50% of the traces for head impulses in a particular plane. VOR gain was considered to be reduced if it was less than 0.80 for lateral and less than 0.70 for RALP and LARP. Descriptive statistics was done to obtain mean, standard deviation and median of VOR gain. The outcomes of descriptive statistics and percentage of individuals with ANSD who had reduced VOR gain and presence of refixation saccade in each canal are mentioned in Table 3.

Table 3.

VOR gain and refixation saccades on lateral, anterior and posterior canals in healthy individuals and individuals with ANSD

Group	Name of semicircular canal	Left							Right						
		Presence of refixation saccades		VOR gain					Presence of refixation saccades		VOR gain				
				Reduced		Mean	SD	Median			Reduced		Mean	SD	Median
		N	N (%)	N	N (%)				N	N (%)	N	N (%)			
ANSD	Lateral	07	35	09	45	0.77	0.18	0.82	04	20	07	35	0.82	0.20	0.89
	Anterior	00	00	06	30	0.71	0.18	0.77	02	10	05	25	0.75	0.13	0.77
	Posterior	03	15	09	45	0.69	0.17	0.71	01	05	09	45	0.68	0.17	0.69
Healthy	Lateral	00	00	01	05	0.92	0.10	0.90	02	10	00	00	1.01	0.11	1.01
individuals	Anterior	01	05	00	00	0.91	0.09	0.90	00	00	00	00	0.96	0.12	0.97
	Posterior	01	05	00	00	0.90	0.11	0.90	02	10	00	00	0.92	0.09	0.91

Note: 'N'- number of individuals; 'SD'- standard deviation; 'VOR'- vestibule-ocular reflex; 'ANSD'- auditory neuropathy spectrum disorders.

vHIT in healthy individuals

All 20 healthy individuals underwent vHIT using lateral, LARP and RALP modules. Figure 8 shows vHIT responses obtained from all 6 semicircular canals and VOR gains for each of them.

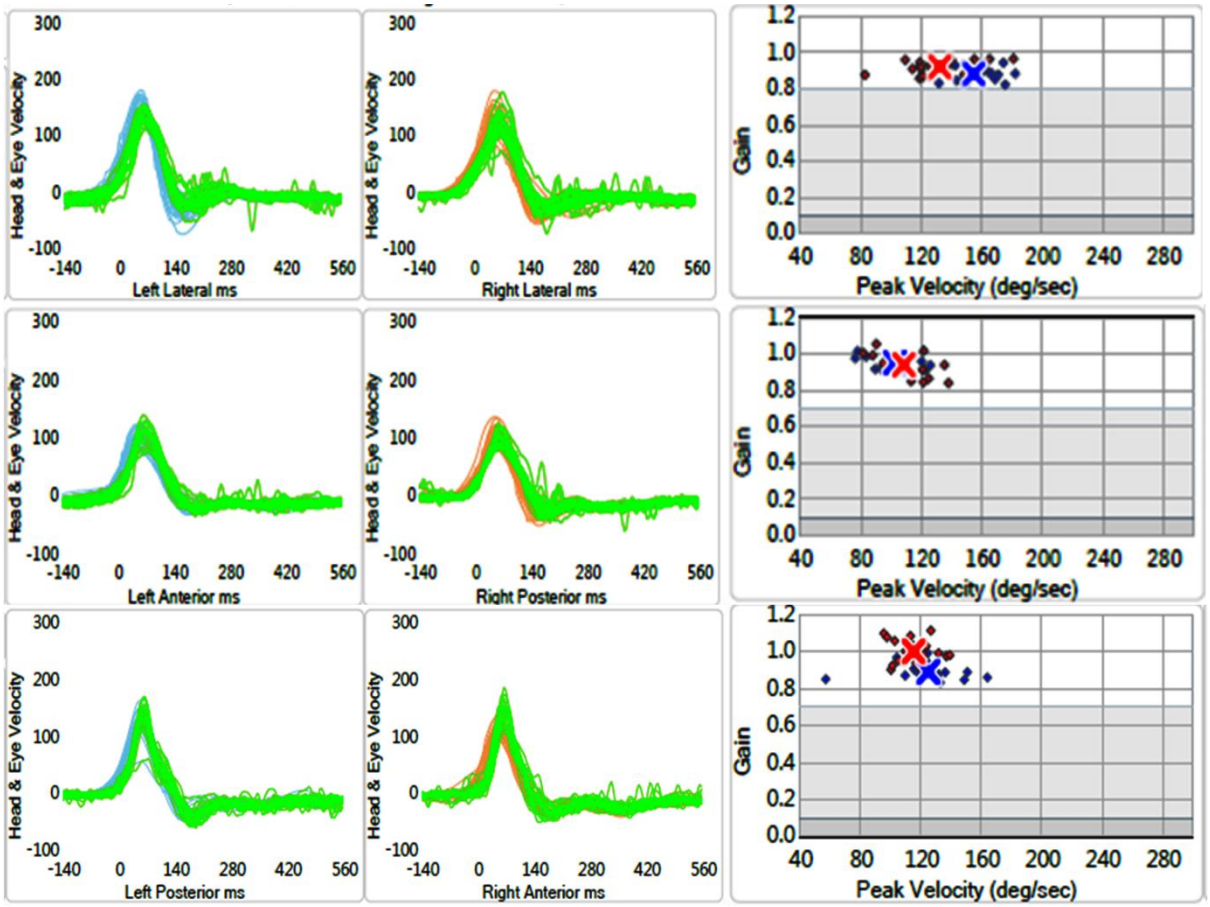

Figure 8: Head and eye velocities and VOR gain for lateral (top panel), RALP (bottom panel) and LARP (intermediate panel) modules obtained from a healthy individual.

Descriptive statistics was done to obtain mean, standard deviation and median of VOR gain. The outcomes of descriptive statistics and percentage of healthy individuals with reduced VOR gain and presence of refixation saccade in each canal are mentioned in Table 3.

Comparison of vHIT between healthy individuals and individuals with ANSD

Refixation saccades were present in 8 (3 bilateral & 5 unilateral), 2 (both unilateral) and 4 (all unilateral) for head impulses in along the plane of lateral, anterior and posterior canals, respectively in individuals with ANSD. In comparison, presence of refixation saccades was observed in 2, 1 and 3 (all unilateral) for head impulses along the planes of lateral, anterior and posterior canals, respectively in healthy individuals. Equality of test for proportions was done to compare the proportion of individuals with refixation saccades in ANSD group to the group of healthy individuals. The results revealed that significantly higher proportion of individuals with ANSD had refixation saccades induced by head impulses along lateral semicircular canal plane than healthy individuals [$Z = 2.19$, $p < 0.05$]. However, there was no significant group difference for head impulses along anterior [$Z = 0.60$, $p > 0.05$] and posterior [$Z = 0.41$, $p > 0.05$] semicircular canals.

Among the 20 individuals with ANSD, reduced VOR gain was evident in 12 (6 bilateral & 4 unilateral), 8 (3 bilateral & 5 unilateral) and 12 (7 bilateral & 5 unilateral) individuals in lateral, anterior and posterior canals, respectively. Among healthy individuals though, only 1 individual had reduced VOR gain (unilaterally) for head impulses in lateral semicircular canal's plane, whereas no one had reduced VOR gain for impulses along the vertical canals' plane. Equality of test for proportions revealed presence of reduced VOR gain in a significantly higher proportion of individuals with ANSD for head impulses along lateral [$Z = 3.18$, $p < 0.01$], anterior [$Z = 3.16$, $p < 0.01$] and posterior [$Z = 4.14$, $p < 0.001$] semicircular canals' planes.

Mann-Whitney U test was done for between groups comparison of VOR gain. Results revealed significantly lower VOR gains in ANSD group compared to healthy

individuals for head impulses delivered along left lateral [Z = -2.34, $p < 0.05$], right lateral [Z = -2.90, $p < 0.01$], left anterior [Z = -3.86, $p < 0.001$], right anterior [Z = -4.49, $p < 0.001$], left posterior [Z = -4.02, $p < 0.001$] and right posterior [Z = -3.93, $p < 0.001$] semicircular canals' planes. Figure 9 shows mean and 95% confidence intervals of VOR gain for head impulses delivered along each of the six semicircular canals' planes.

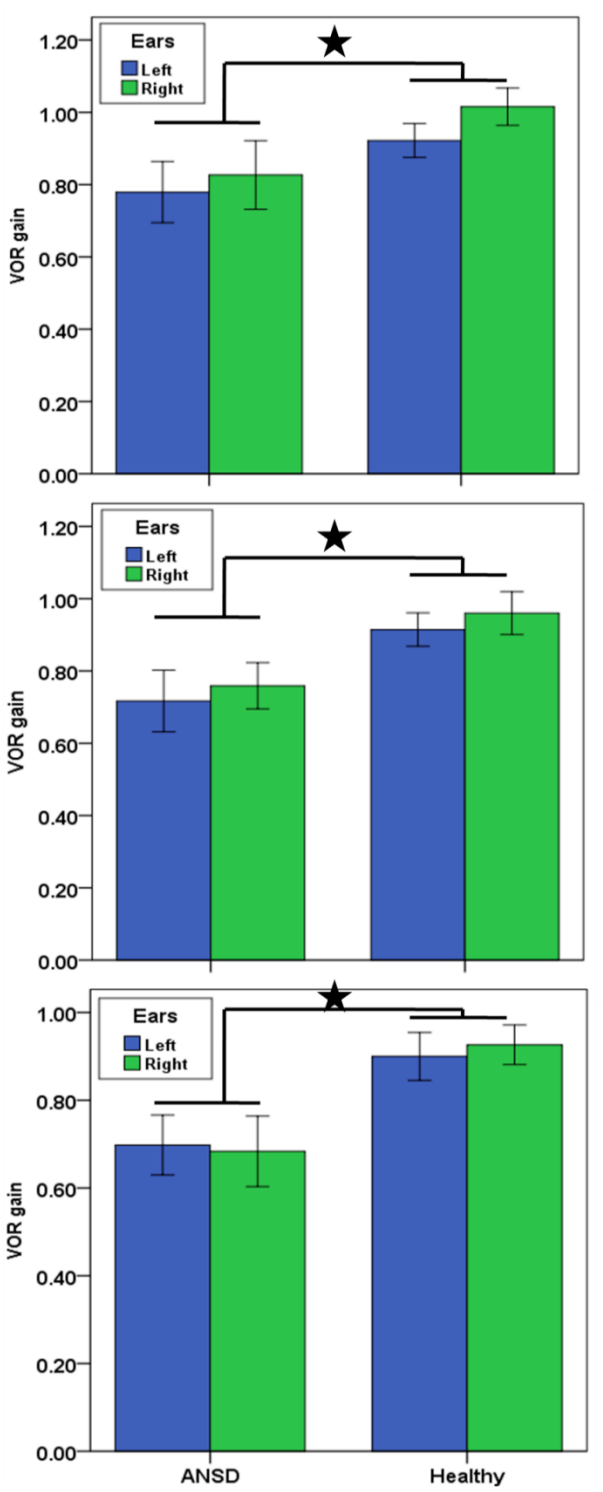

Figure 9: Mean and 95% confidence of VOR gain for head impulses delivered along lateral (top panel), anterior (middle panel) and posterior (bottom panel) semicircular canals' planes and outcomes of Mann-Whitney *U* test for between group comparisons. Star-marked comparisons are statistically significantly different ($p < 0.05$).

Correlation between VOR gain of vHIT and peak-to-peak amplitude of cVEMP and oVEMP

Spearman's correlation analysis was done to study the relationship between VOR gain of vHIT and peak-to-peak amplitudes of cVEMP and oVEMP. The amplitudes of oVEMP were significantly correlated with VOR gain for lateral [ρ = 0.34, $p < 0.05$] and anterior [ρ = 0.39, $p < 0.01$] semicircular canals but not with posterior [ρ = 0.14, $p > 0.05$] semicircular canal. However, there was no significant correlation of cVEMP amplitude with lateral [ρ = 0.15, $p > 0.05$], anterior [ρ = 0.24, $p > 0.05$] and posterior [ρ = -0.05, $p > 0.05$] semicircular canal. Figure 10 shows the regression curves depicting the relationship between VOR gain of vHIT and amplitudes of cVEMP and oVEMP.

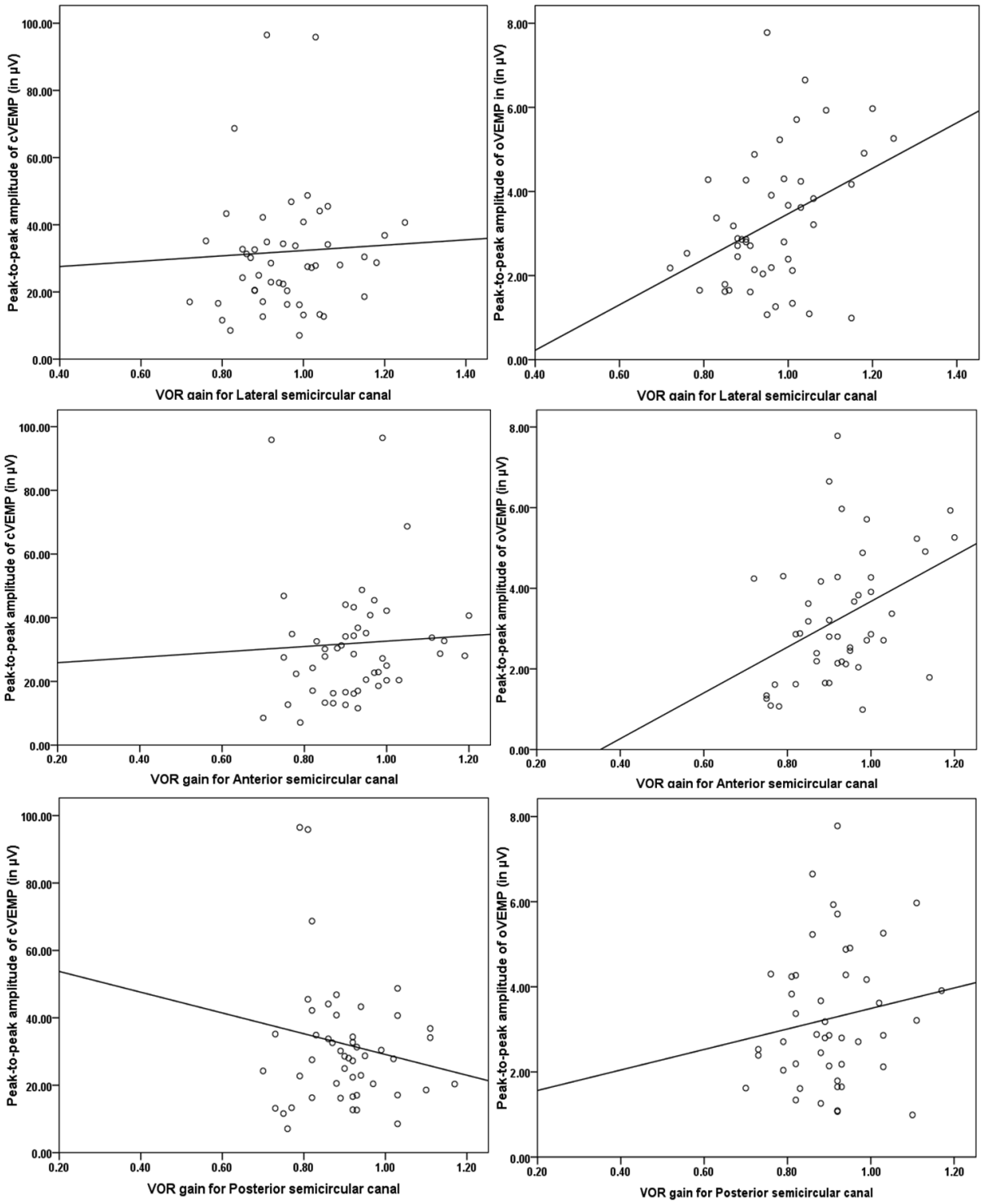

Figure 10: Relationship between peak-to-peak amplitude of cVEMP (left panels) and oVEMP (right panels) and VOR gain for head impulses in the planes of lateral (top panels), anterior (middle panels) and posterior (bottom panels) semicircular canals.

CHAPTER 5

DISCUSSION

Twenty individuals with ANSD and 20 healthy individuals underwent behavioural balance assessment, cVEMP, oVEMP and vHIT. The findings of each of these tests in these two groups and the outcomes of between groups comparison is discussed under separate headings below.

Behavioural tests in individuals with ANSD

In the present study Fukuda stepping test, Romberg test, sharpened Romberg test, tandem gait test, finger-to-nose-test (past pointing test), diadokinetic test (alternate supination & pronation of palm) and tracking shin bone with heel were administered. More than 55% of the participants performed abnormally on Fukuda stepping test, both classical and sharpened Romberg tests and tandem gait test. Relatively fewer participants (≤20%) showed abnormal results on the remaining behavioural tests. While the findings of tests of cerebellar function like finger-to-nose test, diadokinetic test and tracking of shin bone by heel do not find a mention in the ANSD literature, Romberg and Fukuda stepping tests have been done and reported to be abnormal in 66-100% of the individuals with ANSD (Sheykholeslami et al., 2000; Sinha et al., 2012). The findings in the present study therefore represent a smaller proportion of the ANSD contingent with balance deficits depicted behaviourally. The differences in findings of present study to those reported previously could be attributed to the use of small sample sizes by the previous studies which would have eluded the researchers from studying the complete spectrum and thereby caused over estimation of balance deficits in the ANSD population. While Sheykholeslami et al (2000) reported abnormal results on Romberg, Mann and stepping tests in all 3

subjects who were identified with auditory neuropathy, Sinha et al (2012) observed abnormal results on Fukuda stepping test and Romberg test in 2 out of the three individuals with ANSD. The findings of cerebellar tests were not abnormal in most of the individuals with ANSD. This possibly indicates towards a lesser degree of cerebellar involvement or complete sparing or relative robustness of the cerebellar neurons to the effects of neuropathy. Additionally, there could be a case of differences in severity of the pathology. Probably those with abnormal results on the cerebellar tests had more severe forms of neuropathy as these participants also performed poorly on all other behavioural balance assessment tests. However, more elaborate studies with experimental evidences need to be done before reaching any conclusion in this regard.

Behavioural tests in healthy individuals

Abnormal results for the behavioural tests were observed in only 2 (10%) of healthy individuals on Fukuda stepping test, both classical and sharpened Romberg tests and tandem gait test. The remaining tests had all healthy individuals showing normal results. This shows high degree of specificity (90-100%) for the behavioural balance assessment tests. Specificity values of 60-98% have been obtained for Romberg test (Bloem, Grimbergen, Cramer, Willemsen, &Zwinderman, 2001), sharpened Romberg test (Lee, 1998), Fukuda stepping test (Honaker, Boismier, Shepard, & Shepard, 2009), tandem gait test (Cohen, Mulavara, Peters, Sangi-Haghpeykar, Kung, Mosier, & Bloomberg, 2013), finger-to-nose test (Anderson, Mason, Fink, Bergin, Charleston & Gamble, 2005), diadokinetic test (Anderson et al., 2005) and tracking shin bone with heel (Anderson et al., 2005). Therefore, the findings of present study are in congruence with those reported previously in healthy individuals.

Comparison of behavioural balance assessment between healthy individuals and individuals with ANSD

Results of the present study showed abnormal results on Fukuda stepping test, Romberg test, sharpened Romberg test and tandem gait test in significantly higher proportion of individuals with ANSD than healthy individuals. However, there was no significant difference between the groups on cerebellar tests like finger-to-nose test, diadokinetic test and tracking of shin bone by heel. This shows that neuropathy in majority of these participants was isolated to peripheral system and did not affect the cerebellum and its pathways significantly. In fact, ANSD as an entity is known to occur more often as peripheral isolated auditory neuropathy than total neuropathy with central involvement also (Starr et al., 2003). Therefore cerebellar tests are less sensitive to changes caused by ANSD than Fukuda stepping and Romberg test variations.

cVEMP in individuals with ANSD

In the present study the response rate of cVEMP in case of ANSD was 22.50%. Several authors have tried to study the presence of cVEMP in individuals with ANSD and have reported presence of cVEMP to range from 0% to 50% (Sheykholeslami, 2000; Kumar et al., 2007; Sazgar et al., 2010; Sinha et al. 2013, Ismail et al., 2014; Singh et al., 2015). These studies collectively revealed low response rate for cVEMP in individuals with ANSD and thereby indicating sacculocolic pathway dysfunction in these individuals. The response rate of cVEMP in the present study was well within the range reported in the previous studies.

cVEMP in healthy individuals

The present study revealed presence of replicable cVEMP waveforms with a positive and a negative peak in both ears for all the 20 participants (response rate of 100%). This (response rate) and the latencies and amplitude values are in congruence with those observed for EMG normalized cVEMP (Singh & Chithra, 2015; Singh et al., 2016).

Comparison of cVEMP between healthy individuals and individuals with ANSD

In the present study, response rates were significantly reduced in individuals with ANSD than healthy individuals. Further, latencies of cVEMP were prolonged compared to the normal group however, the prolongation attained statistically significant proportions only for P1 latency. Furthermore, cVEMP amplitude was significantly smaller in individuals with ANSD than healthy individuals. Lower response rates, prolonged latencies and smaller amplitudes in subjects with ANSD was also reported previously (Sheykholeslami et al., 2005, Kumar et al., 2007, Sazgar et al., 2010, Sinha et al., 2013; Ismail et al., 2014; Singh et al., 2016). This could be suggestive of a retrolabyrinthine involvement of inferior vestibular nerve in individuals with ANSD as prolonged latencies are suggestive of such pathology (Murofushi et al., 2001). The reason attributed to this finding could be the dys-synchrony or asynchrony of neural firing in the inferior vestibular nerve similar to the auditory branch of the VIIIth nerve (Starr et al., 1996, Kumar & Jayaram, 2006; Singh et al., 2016).

oVEMP in individuals with ANSD

The response rate of oVEMP in individuals with ANSD was found to be 17.50% in the present study The studies done previously in this regard found absence of oVEMP in 90 to 100% of ears with ANSD thereby showing response rates of ≤10% (Sinha, Barman, et al., 2013; Singh et al., 2016). In an unpublished doctoral thesis, Singh (2015) reported presence of oVEMP in 18% (13 out of 72 ears) of the ears of individuals with ANSD. Therefore the response rate of oVEMP in the present study is well within the reports in literature.

oVEMP in healthy individuals

The response rate for oVEMP in healthy individuals was found to be 100%. Air-conduction oVEMP have been reported with 100% response rates by a number of previous studies (Singh & Barman, 2013, 2014; Singh, Valappil, & Mithlaj, 2015; Singh et al., 2016). Further, the latencies and peak-to-peak amplitude of oVEMP in the present study were also found to be well within the range of values reported for these parameters previously (Singh & Barman, 2013, 2014; Singh et al., 2015; Singh et al., 2016).

Comparison of oVEMP between healthy individuals and individuals with ANSD

The response rates of oVEMP were significantly reduced in individuals with ANSD than healthy individuals. Further, latencies of n1 and p1 were significantly prolonged and amplitudes were smaller compared to the healthy group but statistically significant levels were not attained by amplitude values. The findings pertaining response rates and latencies are similar to those reported previously for comparison between individuals with ANSD and healthy individuals (Singh et al., 2016).

However, Singh et al (2016) reported significantly smaller peak-to-peak amplitude in individuals with ANSD than healthy individuals. In the present study, only 20 individuals were evaluated as against 31 in the study by Singh et al (2016). Thus, differences in sample size and heterogeneous nature of the pathology in ANSD could be attributed to the finding of no statistical difference in amplitude between individuals with ANSD and healthy individuals in the present study.

vHIT in individuals with ANSD

In the present study vHIT was performed and parameters evaluated were presence of refixation saccades and VOR gain for lateral, RALP and LARP modules. Reduced VOR gain was observed in 25-30% anterior canals (right & left shown as range here) whereas 35-45% of lateral canals and 45% of posterior canals demonstrated reduced VOR gain. Likewise refixation saccades were observed in 20-35% of lateral canals, 10% of anterior canals and 5-15% of posterior canals. There are no previous studies of vHIT on individuals with ANSD and therefore the findings of the present study are the first in this regard. The findings suggest inability of the eye to exactly remain on the target during head movement. The behavioural manifestation of such a thing could be blurring of vision. Blurring of vision was one of the most common complaints and found to be evident in 8 out of the 31 (about 26%) cases with ANSD in a previous study (Singh et al., 2016). These values are very close to the values of reduced VOR gain in the present study. These findings also suggest that both superior and inferior vestibular nerves are affected in individuals with ANSD.

vHIT in healthy individuals

The results of VOR gain and refixation saccade showed no refixation saccade in any healthy individual and VOR gain was reduced in only one side in one

individual. All others produced VOR gains of >0.80 for lateral canals and >0.70 for the vertical canals. These values are reported to be indication of normal VOR gain (Curthoys et al., 2010), which is what is expected in healthy individuals with no vestibular dysfunction. Further, the values of VOR gain in healthy individuals are very similar and well within the range reported in previous studies for lateral, LARP and RALP modules (McCaslin, et al., 2014;McGarvie et al., Redondo-Martinez et al., 2016).

Comparison of vHIT between individuals with ANSD and healthy individuals

Refixation saccades were evident in significantly higher proportion of individuals with ANSD than healthy individuals for head impulse along the lateral canal but nor for the two vertical canals. Involvement of only one semicircular canal or higher degree of pathology for responses from only one semicircular canal has been shown previously in several vestibular pathologies (Tamutzer, Bockisch, Buffone, Weiler, Bachmann, Weber, 2016). There is also a possibility that significant amount of central compensation has occurred in these subjects and therefore the refixation saccades are not that evident (Curthoys & Macdougall, 2012).

In terms of the VOR gain, significantly higher proportion of individuals with ANSD had reduced VOR gain for each of the three canals than healthy individuals. Also, VOR gain was significantly lower in the group of individuals with ANSD than the group of healthy individuals for all three semicircular canals. There are no previous studies to compare the results against. However, the findings do indicate that a high percentage of individuals with ANSD have both inferior and superior vestibular affected.

Correlation between vHIT and cVEMP and oVEMP

The findings of the present study showed significant positive correlation between oVEMP amplitude and VOR gain of lateral and posterior semicircular canals but not with posterior semicircular canal. Since lateral and anterior semicircular canals are innervated by the fibers from superior vestibular nerve (Fernandez & Goldberg, 1971) and utricle, the generator end organ of oVEMP (Curthoys2010; Manzari, Tedesco, Burgess & Curthoys, 2010; Murofushi, Wakayama & Chihara, 2010; Taylor, Wijewardene, Gibson, Black, Halmagyi, &Welgampola, 2011; Govender,Rosengren& Colebatch, 2011; Lin & Young 2011; Valko, Hegemann, Webber, Straumann, &Bockisch, 2011; Curthoys, Vulovic, &Manzari, 2012), is also innervated by superior vestibular nerve fibers (Fernandez & Goldberg, 1971), correlation between them is as expected. Since posterior semicircular canal is innervated by mainly the inferior vestibular nerve (Fernandez & Goldberg, 1971), the findings of posterior canals did not correlate with the findings of oVEMP.

Correlation analyses between amplitude of cVEMP and VOR gain for head impulses along various semicircular canals revealed no significant correlation between them for any of the canals. This might be attributed to higher degree of variability in the amplitude of cVEMP, as evidenced by high values of standard deviation.

CHAPTER 6

SUMMARY AND CONCLUSION

Auditory neuropathy spectrum disorder is typically associated with normal cochlear function but pathological function of the nerve originating from cochlea. Dysfunction of the vestibular nerve has also been time and again proved through studies using, behavioural balance assessment, bithermal caloric test, cVEMP and more recently oVEMP. However, a wholistic view about the fibres originating from all five end organs (utricle, saccule, & all three semicircular canals) has not been reported upon. In fact there is no study at all describing the findings of nerve fibre originating from posterior and anterior semicircular canals at all. The only objective test that can assess these two canals and the fibres originating in them is vHIT. Therefore, the present study aimed evaluating the fibres beginning at all five vestibular end organs using cVEMP, oVEMP, and vHIT and study the impact of ANSD on body balance.

A total of 20 individuals with ANSD and 20 healthy individuals within the age range of 11-40 years served as the participants. All the participants underwent behavioural balance assessment, cVEMP, oVEMP and vHIT. Behavioural balance assessment included Fukuda stepping test, Romberg test, sharpened Romberg test, tandem gait test, finger-to-nose-test (past pointing test), diadokinetic test (alternate supination and pronation of palm) and tracking shin bone with heel. oVEMP and EMG rectified cVEMP were evoked by 500 Hz tone-bursts presented at 125 dB peSPL and recorded using Biologic Navigator pro evoked potentials system. vHIT was done using lateral, LARP and RALP modules of ICS impulse vHIT system.

Significantly larger contingent of participants with ANSD (≥ 55%) demonstrated abnormal results on Fukuda stepping test, both classical and sharpened

Romberg tests and tandem gait test than healthy individuals ($p< 0.001$). Relatively fewer participants showed abnormal results on the remaining behavioural tests that assess cerebellar function (≤ 25%) and there was no significant difference on these tests between the groups ($p> 0.05$). The individuals with abnormal results on the cerebellar tests had more severe forms of neuropathy as these participants also performed poorly on all other behavioural balance assessment tests. It could be because neuropathy in majority of these participants was isolated to peripheral system and did not affect the cerebellum and its pathways significantly.

Comparison between the groups showed significantly lower response rates, longer latencies and smaller amplitudes of cVEMP in individuals with ANSD (when responses were present) than healthy individuals ($p< 0.05$). Prolonged latencies are suggestive ofretro-labyrinthine involvement of inferior vestibular nerve (Murofushi et al., 2001). Reduced amplitude can be attributed to dys-synchrony or asynchrony of neural firing in the inferior vestibular nerve. (Starr et al., 1996; Singh et al., 2016).

Like cVEMP, the response rate of oVEMP was significantly lower and latencies significantly longer in the ANSD group than in the group of healthy individuals ($p< 0.05$). This further convinces retro-labyrinthine pathology even in superior vestibular nerve fibres originating from utricle (Singh et al., 2015). However, there was no significant difference in amplitude of oVEMP between the groups. This could be attributed to small sample of subjects with presence of oVEMP in the ANSD group in addition to heterogeneity inherent to this population.

In terms of vHIT, individuals with ANSD demonstrated significantly higher prevalence of refixation saccades and reduced VOR gain in all three canal planes than

healthy individuals ($p< 0.05$). This indicates towards dys-synchrony in the firing of vestibular nerve fibres originating from all three semicircular canals.

The findings of the present study showed significant positive correlation between oVEMP amplitude and VOR gain of lateral and anterior semicircular canals but not with posterior semicircular canal. This shows dys-synchrony is affecting superior vestibular nerve originating in the utricle as well as semicircular canals similarly. However, cVEMP did not show significant correlation with VOR gain of any of the three semicircular canals. This might be attributed to higher degree of variability in the amplitude of cVEMP, as evidenced by high values of standard deviation.

Clinical implications

cVEMP, oVEMP and vHIT from all semicircular canals were affected in individuals with ANSD in the present study. This proves beyond doubt that the entire cochlea-vestibular nerve is affected in a large contingent of individuals with ANSD. Further, cerebellar test were not abnormal in majority of individuals with ANSD, which shows that either the cerebellar pathways require lesser synchrony of the nerve fibre firing or are more resistant to the pathology of ANSD. This can be potentially useful in identifying the explicit site of lesion and diagnosis. This study can thereby provide an insight about the vestibular system involvement in patients with ANSD; an understanding of whether or not vestibular nerve fibers from all end organs are affected.

Limitations

The number of participants involved in the study was 20, which poses a limitation to the generalization of the results of the present study to a heterogeneous population like ANSD. Further, refixation saccades were considered to be present when overt or covert saccades were present on more than 50% of the traces for head impulses in a particular plane. This is an operational definition which is randomly selected.

Future direction

Future studies could overcome the above limitations by including larger sample size and measuring refixation saccades objectively. The caloric test can also be included to ensure low frequency response assessment, as vHIT mainly assesses high frequency responses.

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