AUDIOLOGICAL PROFILING AND VOICE CHARACTERISTICS IN INDIVIDUALS WITH EARLY AND LATE-ONSET AUDITORY NEUROPATHY SPECTRUM DISORDER (ANSD)

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This Dissertation is submitted as part

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CERTIFICATE

This is to certify that this dissertation entitled **'Audiological profiling and voice characteristics in individuals with early and late-onset Auditory Neuropathy Spectrum Disorder (ANSD)'** is a bonafide work submitted as a part for the fulfilment for the degree of Master of Science (Audiology) of the student Registration Number: 19AUD028. This has been carried out under the guidance of the faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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This is to certify that this dissertation entitled **'Audiological profiling and voice characteristics in individuals with early and late-onset Auditory Neuropathy Spectrum Disorder (ANSD)'** is the result of my own study under the guidance of Dr. Nisha KV and Dr. Prashanth Prabhu, 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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September 2021

This Dissertation is dedicated to

“Vasudaiva Kutumbakam- My parents,

sister (Purnima) and

brother (Puneet)”

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Abstract

The study aimed to describe onset-based differences using a new parameter, i.e., voice. The onset-based differences in audiological profiling and voice characteristics, the correlation between these two characteristics, and to predict those variables which best segregate the groups based on ANSD- onset is elucidated in the present study. Thirty-one participants (14-31 years) were recruited for the study and were divided into two groups based on onset reported- early-onset group (onset reported to be before 12 years) and late-onset group (onset reported to be during or after adolescence). Audiological profiling was done retrospectively by studying the case report. The participants were asked to record sustained phonation of three vowels (/a/, /i/ and /u/) on smartphones above specific configuration and send the voice sample over email to the experimenter. Acoustic parameters were assessed using Praat software. This was supplemented by perceptual evaluation (CAPE-V) by five speech-language pathologists. Results revealed that the early-onset group had significantly higher PTA and speech thresholds, with more chances of being presented as symmetrical hearing loss. Also, most participants in the early-onset group had a flat configuration of hearing loss, in contrast to the late-onset group, which had a rising type of configuration. The voice analysis results revealed significantly increased fundamental frequency for all vowels and decreased F_2 *and* F_3 *of /i/ in the early-onset group compared to the late-onset group, which can be explained based on differences in the pathophysiology of the disorder. This could also be attributed to the perception-production link; that is, as the perception of high frequency is affected in long-standing ANSD participants, the production of high-frequency sounds is also affected. Although not statistically significant, mean perturbations (jitter and shimmer) and harmonic-to-noise ratio were more affected in the early-onset group reflective of lowered auditory feedback and periodicity in their voice samples. These differences were also complemented by perceptual evaluation findings, which revealed greater severity of pitch, breathiness, strain, hoarseness and overall severity in the early-onset group. It was also found out in the present study that the acoustic and perceptual parameters of voice was mild to moderately correlated with each other. The FLDA analyses revealed that PTA, speech thresholds and configuration were the best predictors of the group differences. In addition, high fundamental frequencies and greater severity in the perceptual rating of voice are predominantly seen in the early-onset group compared to the late-onset group. The presence of such indicators should alert audiologists to reflect on the possible onset of the disorder, which in turn can facilitate their rehabilitation choice.*

Keywords: voice characteristics, onset-based differences, auditory neuropathy spectrum disorder

Chapter 1

INTRODUCTION

Auditory neuropathy spectrum disorder (ANSD) is a retro-cochlear pathology in which the outer hair cell functioning is normal, but the auditory nerve is abnormal (Rance, 2005). Individuals with the disorder are presented with severely abnormal or absent auditory brainstem responses (ABR) and typical otoacoustic emissions (OAE) results (Berlin et al., 2010).

Its prevalence is different across different parts of the world. Rance et al. (1999) reported an incidence of 0.23% of children with high risks of developing ANSD in Melbourne, Australia. They also reported that 11% of the infants and young children with permanent hearing loss had ANSD. Talaat et al. (2009) reported that 13.4% of infants and young children with severe to profound hearing loss were diagnosed with ANSD in parts of Egypt. Sininger (2002) reported the same as 10% in children with varying degrees of hearing loss in the United States. Similar prevalence studies have been done in India. Kumar and Jayaram (2006) reported that 1 in 183 individuals with sensorineural hearing loss had ANSD, including children, adults and geriatrics in and around Mysore District, Karnataka. They also reported a female to male ratio of 2:1. Mittal et al. (2012) reported the prevalence of 26 in 183 children below 12 years, fulfilling the diagnostic criteria of ANSD in New Delhi. Vignesh et al. (2016) reported that out of 217 children ageing six months to 12 years, 11 individuals (5.06 %) had ANSD in and around the regions of Chennai, Tamil Nadu.

This hearing disorder has been identified in all ages, from newborns to adults. However, in early literature, reported in the western context, the onset was predominantly seen in children below ten years (Boudewyns et al., 2016; Zhang et al., 2016). In contrast, studies after 2003 reported late-onset ANSD. Shivashankar et al. (2003) reported the onset of the problem during the first and second decade of life in all the 24 patients they studied (except one who had an onset at the age of 44 years). Similarly, Kumar and Jayaram (2006) reported that 59% of their 61 patients with ANSD had onset between 14 to 24 years of age. Similarly, though rare, scanty reports on late-onset ANSD were reported in western literature, too (Berlin et al., 2010; De Siati et al., 2020; Norrix & Velenovsky, 2014).

The site of lesion of ANSD is supposed to be presynaptic (inner hair cells), synaptic (ribbon synapses) or postsynaptic (dendrites, axons, myelin sheath, ganglion cells, auditory nerve) (Rance & Starr, 2015). Amatuzzi et al. (2011) showed ANSD resulting from selective loss of inner hair cells in premature infants with elevated/ absent ABR. However, isolated inner hair cell losses sparing the outer hair cells are not very common and are not confirmed by temporal bone studies. Synaptic cause resulting from mutations in otoferlin (OTOF) includes affected ribbon synapse due to which the release of Glutamate neurotransmitter is impaired (Moser et al., 2013). Postsynaptic sites of lesion include disorders of auditory nerve function that can occur at (i) unmyelinated dendrites within the cochlea; (ii) myelinated dendrites and axons coursing centrally; and (iii) myelinated auditory ganglion cells. Rance and Starr (2015) define six putative sites for testing patterns defined as "auditory neuropathy", as shown in Figure 1.1

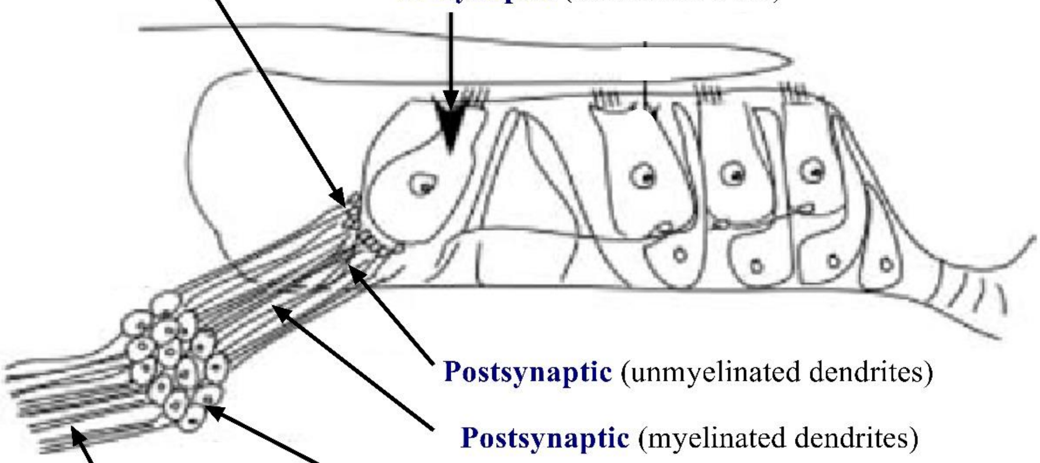

Figure 1.1. Six putative sites for ANSD (adopted from Rance and Starr, 2015)

The site of lesion (Figure 1.1) decides the audiological finding/ clinical signs on electrophysiological tests. The amplitude of summating potential reduces for presynaptic lesions, with either absent/ elevated ABR peaks (Amatuzzi et al., 2011). This is associated with the presence of Otoacoustic Emissions (OAEs) and Cochlear Microphonics (CM). Synaptic Lesions results in abnormal Compound Action Potentials (CAP) reflecting the dysynchrony of activation of auditory nerve terminals and elevated/ absent ABRs (Santarelli et al., 2008, 2015). Normal summating potentials and OAEs in cases with synaptic lesions results due to intact inner and outer hair cells, respectively. Postsynaptic Lesions to the dendritic nerve terminals, axons, ganglion cells, or auditory nerve result in similar findings like ribbon synapse disorders, that is, normal summating potentials with abnormal/ absent nerve responses (CAPs) (Rance & Starr, 2015).

Apart from findings of electrophysiological tests, ANSD cases also show some differentiating signs in behavioral measures. Kumar and Jayaram (2006) reported the audiometric configuration to be peaked type, with a peak at around 2000 Hz. This was supported by the fact that apical fibres, corresponding to low frequency, are the longest and most prone to damage than basal fibres, which correspond to high-frequency sounds. The mid fibres are the shortest and, thus, affected least, giving better mid-frequency thresholds than other frequencies. Based on the clinical signs and symptoms, Berlin et al. (2010) divided the 260 ANSD subjects in his study into six clinical sub-groups, as shown in Table 1.1.

Table 1.1

Classification of ANSD based on the audiological characteristics in accordance to Berlin et al. (2010).

Category	***Hearing sensitivity***	***OAE***	***Cochlear microphonic***	***ABR***	***Child/Adult***
Category 1	Normal	Normal	Present	Absent	Children
Category 2	Severe to profound	Present (initially)	Present (initially)	Absent	Children
Category 3	Severe to profound	Absent	Present	Absent	Children
Category 4	Profound	Absent	Absent	Absent	Adults
Category 5	Normal at birth but develop HL later	Normal	Present	Absent	Children/Adults
Category 6	Normal	Normal	Present	Absent	Adults

Note: HL: Hearing Loss, OAE: Otoacoustic Emissions, ABR: Auditory Brainstem Response

As seen in Table 1.1, Berlin et al. (2010) reported that audiological characteristics of the individuals varied across a continuum, with auditory abilities of the ANSD individuals ranging from mild to severe. While the authors acknowledged that some individuals with ANSD went unidentified or had no complaints about hearing until sometime between puberty and adulthood in the western context. Shivashankar et al. (2003) reported a similar late onset pattern (23 patients, between the age range of 13 to 49) in Indian population. The onset and audiological characteristics crucially distinguish these groups, both of which in turn depends on aetiology. Early-onset was associated with hyperbilirubinemia, ototoxic drug regimen, low birth weight, low APGAR scores, anoxia, and family history of deafness (Berlin et al., 2003). These causes are not associated with late-onset ANSD. Prabhu et al. (2012) reported that Late-onset ANSD cases did not have any pre-, peri or postnatal causes; instead, some predisposing factors were associated with those individuals. These factors include exposure to toxic chemicals (pesticides) and toxic solvents (Xylene), low socioeconomic status and hormonal variations, which were present soon after puberty. Draper and Bamiou (2009) reported that exposure to Xylene was noted in late-onset auditory dys-synchrony. Clinical symptoms seen in late-onset patients were vertigo, headache, tinnitus, defective vision and difficulty understanding speech. Late-onset patients tend to show a rising configuration of hearing loss due to more affected apical nerve fibres, compared to early-onset ones, which show flat loss due to degradation of apical fibres followed by basilar region. Jijo and Yathiraj (2012) reported a low positive correlation (r =0.27 and 0.32 in the right and left ear respectively) between the age of onset of ANSD and degree of hearing loss, while a low negative correlation (r=-0.23 and -0.21 in the right and left ear respectively) was observed between the age of onset and speech identification scores.

Although the onset-based heterogeneity in ANSD patients is usually explored using the above-cited manifestations, all these studies on late-onset are primarily conducted retrospectively using only the target (late-onset) population, limiting the scope of any comparisons with early-onset related manifestations. While onset related distinctions are often described for explanatory purposes in these studies, a direct inference cannot be made as they lack experimental control, which can only be made in prospective designs. The retrospective nature of case reports or studies fundamentally limits direct comparisons of population characteristics of late-onset and early-onset groups. Further, late-onset diagnosis in these cases is dependent on the patient complaints documented in case history (Berlin et al., 2010). However, if the patient reports of onset of symptoms in late adulthood, lack of audiological reports in these patients at childhood substantiating normal auditory functions in earlier years cannot be ruled out. Further, questions regarding the efficacy of newborn hearing screening and primary infrastructure for audiological testing in developing countries (Gupta et al., 2015; McPherson, 2012), where the late-onset cases are reported, makes the research strides (comparison of late versus early-onset characteristics) in this direction even more challenging.

A very few studies reported voice characteristics in individuals with ANSD. Maruthy et al. (2019) observed deviant voice characteristics (rough voice, breathiness, strain, high pitch and reduced loudness) in long-standing ANSD patients. They reported that the voice characteristics were affected for individuals having an onset of the problem for more than five years. Thus, late-onset patients with more prolonged onset also showed deviant voice parameters. There are no reported literatures comparing the voice characteristics of early and late-onset ANSD patients. The difference in the audiological characteristics between the two groups is still unclear. The early and late-onset groups have never been compared in these aspects. Thus, this study would be the first of its kind in those objectives.

1.1 Aim of the study

To compare the audiological profiles and voice characteristics of early and late-onset ANSD patients.

1.2 Objectives of the study

The specific objectives of the study are:

(a) To compare audiological profiles of early and late-onset ANSD groups.

(b) To compare the differences (if any) in voice characteristics between the two groups using measures such as voice quality, fundamental frequency, formants, harmonic-to-noise ratio and perturbation (jitter and shimmer)

(c) To correlate audiological findings and voice characteristics of participants within the group.

(d) To predict the audiological and voice factors which best segregate the two groups.

1.3 Null Hypotheses

The following null hypothesis will be tested in the research proposed.

(a) There is no difference in the audiological profile between early and late-onset ANSD groups

(b) There is no difference in the voice characteristics between early and late-onset ANSD groups

(c) There is no correlation between the audiological and voice characteristics of participants within each of the two groups.

(d) Audiological and voice parameters cannot be used to segregate the two groups.

Chapter 2

REVIEW OF LITERATURE

Auditory neuropathy spectrum disorder (ANSD) is a condition described first by Starr et al. (1996) as a disorder characterized by absent or abnormal ABR, with intact outer hair cells functioning, as evident by the presence of otoacoustic emissions and cochlear microphonics. The possible site of lesion could be inner hair cells, synapses between inner hair cells and auditory nerve or the auditory nerve itself (Buchman et al., 2006; Rance et al., 2002). The presence of normal OAE and a corner audiogram indicate either complete IHC loss or absence of auditory nerve (Amatuzzi et al., 2011; Buchman et al., 2006; Varga et al., 2003). In contrast, a lesser degree of hearing loss indicates intact IHC functioning and compromised neural functioning (Starr et al., 1996). Based on the onset, ANSD can be divided into early or late-onset ANSD.

2.1 Age of onset

Berlin et al. (2010) profiled 260 ANSD patients evaluated in Michigan, USA. In contrast to the eastern study, this study reported that 86% of the participant had a mean age of onset below 12 years. In contrast to western studies (Berlin et al., 2010; Starr et al., 2000, 2001), which observed that ANSD was primarily seen in the pediatric population, Indian studies (Jijo & Yathiraj, 2012; Kumar & Jayaram, 2006; Shivashankar et al., 2003) found that that age of onset of ANSD in different parts of India is usually at, or after the pubertal age. Kumar and Jayaram (2006) reported the mean age of onset to be 16 years in their register-based study of 3 years. The age of onset was reported to be 14-24 for the maximum number of participants. Shivashankar et al. (2003) reported the mean age of onset to be 17.6 years in their retrospective study of 11 years (1990-2001). A similar onset of ANSD was reported by Jijo and Yathiraj (2012) in their retrospective survey of 2 years (2008-2010), where they reported the age of onset to be in the age range of 10-20 years. Narne et al. (2014) studied 198 ANSD individuals retrospectively between September 2000 and June 2012. The mean age of onset reported was 21.03 years ± 9.89. 82% of the participants were at the onset of the disorder in adolescence and adulthood.

2.2 Etiology

This section would deal with the differences in etiology based on the onset of ANSD. Early-onset ANSD is usually secondary to the pre, peri or post-natal risk factors, whereas these risk factors are usually not present in late-onset ANSD.

Early-onset ANSD. Early-onset ANSD is usually secondary to hyperbilirubinemia (Berlin et al., 2010; Rance et al., 1999), ototoxic drugs, low birth weight, low APGAR scores, anoxia and positive family history (Berlin et al., 2003). These pre, peri and post-natal complications might directly or indirectly affect the functioning of the auditory nerve, inner hair cells or the synapse between the two, leading to ANSD. Berlin et al. (2010) reported hyperbilirubinemia (48%), premature birth (47%), exchange transfusion (28%), ototoxic drugs (28%), respiratory distress (15%) and anoxia (17%) as an etiology of early-onset ANSD.

Late-onset ANSD. Draper and Bamiou (2009) reported a case of late-onset ANSD secondary to xylene exposure. Xylene is a type of organic solvent found in household items such as paints, adhesives, cleaners, pesticides, etc. These solvents have been shown to affect the peripheral hearing along with the central auditory pathway (Metrick & Brenner, 1982; Morata et al., 1993). This was suggested due to the lipo-solubility of xylene and other solvents. This is meant to damage the peripheral receptor structures by affecting their membrane integrity and also affect the synapses through peripheral receptors. This alters the stimulus transduction mechanism (Abbate et al., 1993).

Cianfrone et al. (2006) reported a case of temperature-dependent ANSD, where the audiological characteristics matched with those of ANSD when the core body temperature rose in response to fever, stress or intensive activity. The patient starts responding normally as soon as the body temperature decreases. Audiological findings associated with high body temperature were temporary threshold shift, poor speech discrimination, reduced contralateral suppression of otoacoustic emission and absent ABR. This was attributed to the pathogenesis as a rise in temperature could lead to a conduction block in demyelinating peripheral nerve fibres. This is due to the fact that increasing temperature may lead to the inactivation of voltage-dependent sodium channels, which eventually results in failure of a generation of any impulse (Davis, 1970; Mcdonald & Sears, 1970; Rasminsky, 1973).

Prabhu et al. (2012) reported another predisposing factor of late-onset ANSD. This includes the low socioeconomic status of participants having late-onset ANSD. Most of the participants or caregivers of their study depended on agriculture as their main source of income. These farmers are very commonly exposed to pesticides. The toxic substance present in pesticides could be the major etiology for late-onset ANSD, especially in India, where the maximum share of the population has the primary occupation as agriculture. They also reported exposure to toxic solvents such as xylene and toluene as another predisposing factor of late-onset ANSD.

Leonardis et al. (2000) reported Hereditary Sensory and Motor Neuropathy as a potential etiology for acquired auditory neuropathy in a European gipsy family. This disorder was characterized by atrophic muscles of extremities, affected sensory modality of distal limbs, mildly impaired pupillary response to light, severe skeletal deformities and sensorineural deafness. This disorder is characterized by low motor nerve conduction velocity. The mutation was reported in chromosome 8q24.

Rance et al. (2012) reported of Charcot- Marie tooth (CMT) disease as a cause of auditory neuropathy in children with a confirmed diagnosis of CMT- 1 (demyelinating neuropathy) and CMT- 2 (Axonal form) by genetic testing. The pathogenesis was reported to be reduced conduction velocity in the CMT- 1 group, whereas a decreased number of fibres (axonopathy) in CMT-2. The participants of their study had reduced ability to detect modulations at a rapid rate (suggesting temporal processing deficit) and decreased speech perception in noise. Similar results were found in patients with Friedrich Ataxia, where the temporal processing ability and speech perception in noise was decreased due to the auditory pathway disruption, which was likely to be secondary to axonal degeneration.

Manchaiah et al. (2011) reported genetic markers linked to non-syndromic ANSD. They reported AUNA1 and PCDH9 as the gene markers for autosomal dominant type of inheritance, OTOF, DFN895 and GJB2 for an autosomal recessive type of inheritance and AUNX1 for X-linked type of inheritance. They have pointed the importance of genetic screening for early identification of the disorder and deciding the best treatment option. The detected mutation can help in identifying the site of pathology, for instance, if the mutation is in the otoferlin gene, which encodes protein Otoferlin which is, in turn, expressed in inner hair cells. This inner hair cells damage can be managed better with a cochlear implant than hearing aids (Varga et al., 2003). Narne et al. (2014) reported the etiology in their late-onset participants to be ataxic motor neuropathy, muscular dystrophy vascular neuropathy, Friedrich's ataxia, traumatic injury, post-mumps and post-seizures.

2.3 Audiological Characteristics in individuals with ANSD

This section would deal with the differences in audiological characteristics (degree and configuration of hearing loss) based on the onset of ANSD. A run-through of the literature suggests that the early-onset ANSD is associated with greater severity of hearing loss along with flat configuration in opposed to late-onset ANSD, which is associated with a lesser degree of hearing loss with rising or peaked type of audiometric configurations.

2.3.1 Degree

ANSD is usually presented with varying degrees of hearing loss, ranging from normal hearing sensitivity to profound hearing loss (Berlin et al., 2010; Rance et al., 2010; Starr et al., 2000). The threshold of audibility fluctuates with respect to the duration of the disorder and individual variability (Kumar & Jayaram, 2006; Narne et al., 2014; Rance et al., 1999). Speech identification scores are measured between 0 to 100% in this cohort (Berlin et al., 2010; Kraus et al., 2000; Kumar & Jayaram, 2006). Most patients do not exhibit any correlation between speech perception scores and behavioural thresholds (Kumar & Jayaram, 2006; Zhang et al., 2016). Though the degree of hearing loss ranged from normal to profound in their study, Narne et al. (2014) reported that the maximum number of participants showed mild to moderate degree of hearing loss (54%) and a rising type of configuration of hearing loss (78%). Similar results were reported in other studies (Berlin et al., 2010; Jijo & Yathiraj, 2012), that is, the maximum number of participants in these studies were reported of being presented with mild to moderate degree of hearing loss.

Shivashankar et al. (2003) studied the severity of hearing loss in patients having ANSD for lesser duration (less than five years) versus those having long-standing ANSD (greater than five years). They reported that the earlier group had a mild degree of hearing loss, whereas a moderately severe to severe degree of hearing loss was seen in most patients in the latter group. Thus, a progression of disorder was noted with respect to duration. This progression was also seen for speech identification scores, where the scores decreased with an increase in the duration of the disorder. Starr et al. (1996) found similar deteriorating results with respect to the duration of the disorder. A similar correlation between duration of disorder and degree of hearing loss and duration of disorder with speech identification scores were found by Jijo and Yathiraj (2012). They reported a significant low positive correlation between duration of disorder and degree of hearing loss in both ears. They also found a significant low negative correlation between duration of disorder and speech identification scores for both ears.

2.3.2 Configuration

Jijo and Yathiraj (2012) compared the audiological findings of ANSD patients who reported the duration of disorder as lesser versus longer. They concluded that participants with lesser duration of disorder had peaked/ rising configuration, whereas those with longer duration had a flat audiometric configuration. They have attributed this finding to the fact that low-frequency fibres have longer courses (Arnesen & Osen, 1978), making them more susceptible to neuronal pathologies than mid-frequency and high-frequency fibres, which are generally shorter. Thus, in the initial stage, the client is presented with a peaked/ rising configuration, which later progresses to a flat type, as shorter mid and high-frequency fibres are also affected.

Kumar and Jayaram (2006) also reported that the maximum number of participants of their study had a peaked type of audiometric configuration. They also reported the correlation between the configuration of audiogram and speech identification scores. They reported SIS to be more for individuals having peaked/rising audiogram than those having other types of configurations (saucer, sloping or flat). This was explained by the fact that mid-frequencies contribute maximum to speech perception. Thus, patients with a peaked type of audiogram with a lesser amount of hearing loss at mid-frequencies compared to other frequencies had more SIS than their counterparts. They also hypothesized that the extent of temporal disruption could be detected with the amount of low-frequency hearing loss. They assumed that there is an inverse relationship between the two, which reduces the speech perception abilities in those individuals with more hearing loss at low frequencies.

2.4 Voice Characteristics in individuals with ANSD

Auditory deprivation is known to cause deterioration in segmental as well as supra-segmental aspects of speech. Coelho et al. (2015) have summarized the effects of types, severity and onset of hearing loss on voice characteristics. Individuals with Sensorineural hearing loss (SNHL) are reported to be having either high fundamental frequency (Campisi et al., 2005; Evans & Deliyski, 2007; Higgins et al., 1994) or fundamental frequency within normal limits along with normal jitter and shimmer (Van Lierde et al., 2005).

Though there is a scarcity of researches in voice characteristics of ANSD (Maruthy et al., 2019), studies have been done on individuals with mild to moderate hearing loss, which is supposed to be the most probable degree of hearing loss in individuals with ANSD. Behlau et al. (2010) reported resonance disorders in individuals with mild to moderate degrees of hearing loss, whereas high fundamental frequency is reported in individuals with severe to profound hearing loss (Coelho et al., 2015; Higgins et al., 1994; Lee et al., 2013).

Based on the onset of disorders, different researchers have found varying degrees of vocal distress. However, these studies are done on individuals with sensorineural deafness. These differences in voice are also dependent on the onset of the pathology. Evans and Deliyski (2007) studied vocal characteristics of pre-lingual deaf adults. They reported that these individuals had high variability of the fundamental frequency, excessive intonation and pitch variation, increased loudness and irregularities in resonance. Lane and Webster (1991) did a similar study but with post-lingual deaf adults. They reported fundamental frequency to be more variable in this cohort. Mora et al. (2012) assessed the voice of post-lingual severe hearing loss individuals and reported the voice to have high jitter, shimmer, harmonic-to-noise ratio and fundamental frequency. They also reported more instability of loudness. Wirz et al. (1981) pointed out the perceptual differences in the voice of individuals with hearing loss. They have reported the voice of the pre-lingual deaf to be hoarse, breathy and more strained, whereas the voice of post-lingual deaf was reported to have abnormal intonation, though the perceptual voice quality was better than pre-lingual deaf individuals. However, all these onset-based differences are reported for sensorineural hearing loss.

These onset-based differences also exist for ANSD, as the extent of pathology differs with the onset. The deterioration in speech production in individuals with hearing loss subsequent to ANSD are reported due to compromised the auditory feedback (Maruthy et al., 2019). This auditory feedback helps to check the accuracy of speech output and adjust the speech motor behaviour accordingly. Zimmermann and Rettaliata (1981) reported the cause of speech deterioration in individuals with hearing loss to be the over-learnt motor pattern. This could be the reason for deteriorated voice in pre-lingual individuals. Maruthy et al. (2019) studied voice characteristics of long-standing ANSD, which is the only reported study having this objective. The study included 11 participants (seven females and four males) within the age range of 17-30 years. Perceptual voice evaluation was done in these patients by certified Speech-Language Pathologists using the CAPE-V (Consensus Auditory Perceptual Evaluation of Voice) visual analog scale. These perceptual scores were compared with those of the control group, which consisted of 20 age-matched participants. They reported the voice of long-standing ANSD patients to be rough, strained and breathier. They also reported their voice to be of high pitch and less loudness. They showed a positive correlation between the duration of the disorder and perceptual rating of voice quality in these individuals. The researchers have hypothesized that the deterioration of voice depends upon the extent of dys-synchrony rather than the amount of hearing loss. The reason for ANSD individuals having a softer voice was given as low confidence in these individuals secondary to their perceptual deficits.

The assumption that ANSD individuals would have similar differences in the voice as individuals with sensorineural deafness is yet to be proven experimentally due to a lack of research in the voice domain in the ANSD population. Thus, the differences in the voice-based on pathology are still the research need. Based on previous evidence, we hypothesize that late-onset ANSD patients are likely to show less deviant voice characteristics than those in the early-onset ANSD group. This study would be the first of its kind to describe the ANSD onset related vocal manifestations in early and late-onset ANSD patients. The specific objectives of the study are to compare the audiological profiles and differences (if any) in acoustic (fundamental frequency, formants, harmonic-to-noise ratio, jitter and shimmer) and perceptual voice characteristics between the early and late-onset groups with ANSD, along with the correlation between these parameters.

Chapter 3

METHOD

This chapter deals with participants' characteristics, informed consent and ethical considerations, retrospective audiological profiling, the procedure of voice samples recording, parameters taken for voice analysis (acoustic and perceptual) and statistical analyses used. The study uses a retrospective and experimental comparative type of research design for audiological profiling and voice characteristics, respectively.

3.1 Participants

A total of 31 participants, aged 14-31 years, diagnosed with bilateral auditory neuropathy spectrum disorder (ANSD) by the Rehabilitation Council of India (RCI) certified Audiologists were considered for the study. The criteria adopted to diagnose ANSD in the Audiology clinic were those recommended by Starr et al. (2000): absent or abnormal ABRs (delayed in latency or attenuated in amplitude), presence (average or robust amplitude) of OAEs and absent middle ear reflexes. Based on the clinical record, the diagnosis of ANSD was confirmed by a Neurologist using clinical examination and Computerized Axial Tomography/ Magnetic Resonance Imaging.

The participants were divided into two groups based on the onset of the ANSD symptoms: early-onset (n=15, eleven females, four males, mean age= 22.07 y ± 3.75) and late-onset (n=16, eleven females, five males, mean age= 22.13 y ± 3.98). A cut-off criterion of 12 years for the group segregation was considered in the study, based on the recommendations of Centres for Disease Control and Prevention (CDC).

Participants who were diagnosed as ANSD in childhood (6-10.2 years) with the problem reported at birth (reported and assessed at the institute between 2005 and 2011) were considered for the former group, while the latter group comprised of adults who were diagnosed as ANSD at the age of > 12 years, with no complaints of auditory deficits in childhood (reported and assessed between 2013 and 2020). Caution was taken to include only participants with the onset of lesser than five years duration in the late-onset groups, as long-standing ANSD adversely affects vocal characteristics (Maruthy et al., 2019). Also, to rule out any language problems, Clinical Evaluation of Language Fundamentals (CELF-4) (Semel & Wiig, 1980) was administered on late-onset patients, who were included only if the language skills were age-appropriate.

3.2 Informed consent and ethical considerations

Informed consent was taken from all the participants, where each subject was informed about the objective of the study and its need in brief. The anonymity of the participants was maintained throughout the study. The willingness of any patient to participate in the study did not affect their routine audiological assessment and other evaluations. All procedures performed in this study adhered to the bio-behavioural research standards (Venkatesan & Basavaraj, 2009) framed by the institutional ethical review board, whose permission was obtained for the study.

3.3 Audiological Profiling

The data collection for audiological profiling was done retrospectively by studying the case reports from the medical records section, Department of Clinical

Services (DCS), AIISH Mysore. The audiological profiling included pure tone audiometry, degree of hearing loss, configuration of hearing loss, speech thresholds (speech recognition thresholds/ speech detection thresholds), the symmetry of hearing loss and presence of cochlear microphonics, as seen in Table 3.1.

Table 3.1:

Different Audiological tests with their protocols and instrumentation used.

Audiological Test/ Variable	**Instrumentation**	**Protocol/ Material to be used**
Pure Tone Audiometry	Calibrated dual-channel diagnostic audiometer: GSI-61 (Grason-Stadler Inc.) and Piano Inventis (Inventis SRL Inc.)	250-8000 Hz for air conduction and 250-4000 Hz for bone conduction using a modified version of the Hughson-Westlake procedure (Carhart & Jerger, 1959). The pure-tone average was calculated using four frequencies (500-4000 Hz)
Degree of Hearing Loss		Goodman (1965) classification from normal to profound hearing loss (including minimal degree of hearing loss)
Configuration of Hearing Loss		Pittman and Stelmachowicz (2003) classification of audiometric configurations was adopted, where the configuration of hearing loss can be divided into rising, sloping, flat, u-shaped, tent-shaped and others.
Speech Thresholds (SRT/SDT)		Language-specific (Kannada) spondee words (Rajashekhar, 1976)
Cochlear Microphonics (CM)	Clinical AEP systems: Biological Navigator Pro (Natus Medical Inc.) and SmartEP (Intelligent Hearing Systems)	Stimuli: Clicks; presentation level: 80-90 dB SPL, 1500-2000 sweeps, repetition rate: >30.1/s, Transducer: Insert Receivers; amplification:1,00,000 times, Epoch: 10 ms, band-pass filter: 300 to 1500-3000 Hz, presence of CM was confirmed with both rarefaction and condensation polarity followed by alternating polarity.

3.4 Voice Characteristics

After screening medical records, the short-listed participants were contacted over the telephonic interview to assess their language skills (as discussed in inclusionary criteria) and voice characteristics. The participants were asked to record sustained phonation of vowels /a/, /i/ and /u/ and send the recorded voice samples over email. To facilitate the understanding of the task, a recorded video of the instructions and a sustained phonation sample enacted by an Indian male speaker was sent for participant viewing. Smartphones above specific configurations (Android 4, CPU frequency > 1.3 GHz) were used for recording purposes (Manfredi et al., 2017). Uloza et al. (2015) showed that smartphones are reliable in assessing acoustic voice parameters.

The rationale for including the online-based data collection stemmed from the need for social distancing and alternative assessment procedures during the COVID-19 crisis. The use of alternative methods rather than conventional voice assessment in the COVID-19 pandemic for voice assessment (Jannetts et al., 2019; Lin et al., 2012; Maryn et al., 2017) has become increasingly efficacious as they offer both accessibility and safety. To further validate the utility of the online-based recordings to the conventional voice sample recordings, a pilot study comprising of voice samples of 5 normal adults (18 – 25 y) was carried out using both methods. The adults were asked to phonate /a/. A smartphone of Android 8 and CPU Frequency of 2.05 GHz was used for online recording, while the offline analyses were carried out using Computerized Speech Lab (CSL, Kay Elemetrics, 1996) module. The vocal parameters used in the current study were compared between the two recording modes using Mann-Whitney U test, which showed no statistically significant difference ($p > 0.05$) between the recordings on all the parameters considered (fundamental frequency: /z/=0.31, p=0.75, F1: /z/=0.10, *p*=0.92, F2: /z/=0.32, *p*=0.75, F3: /z/=0.94, *p*=0.35, jitter: /z/=0.11, *p*=0.92, shimmer: /z/=1.05, *p*=0.29, HNR: /z/= 0.73, *p*=0.47).

To monitor the environmental noise, an android based application Sound Meter, developed by Smart Tools Company (Ibekwe et al., 2016), was used at the participants' end. Live monitoring of the online recording session was supervised by the experimenter through an online video call. The participants were also asked to send the environmental noise data throughout the recording, which the experimenter further analyzed before including the voice sample. Samples with environmental noise less than 45 dB SPL were included for analysis (Lebacq et al., 2017).

3.5 Voice Analyses

The noise-free voice samples obtained were subjected to both acoustic and perceptual analyses. The acoustic parameters of voice were assessed using the Praat software (Boersma & Weenink, 2010). The waveform segment where the amplitude remained constant with respect to time was extrapolated from the recording, and analysis was done. Fundamental frequency (F_0) along with the first three formant frequencies (F_1, F_2 & F_3) were computed for each recording using the pitch menu in Praat software. Jitter, shimmer and harmonic-to-noise ratio were also calculated using the Point-process option in Praat Software, which assess the parameter based on the sequence of points defined with respect to time. Burris et al. (2014) concluded that fundamental frequencies and harmonics generated by Praat Software were reliable, accurate and were comparable to the values obtained in acoustic analysis using other software packages such as WaveSurfer (Sjölander & Beskow, 2005), TF32 (Time-

Frequency analysis software) (Milenkovic, 2010) and Computerized Speech Lab Module (CSL, Kay Elemetrics, 1996).

Subjective voice quality ratings were obtained from five certified Speech-language pathologists (SLPs), who were asked to perceptually rate the voice samples using a standardized voice assessment scale - Consensus Auditory Perceptual Evaluation of Voice (CAPE-V, Kempster et al., 2009). The SLPs listened to the voice recording on Sennheiser HAD 200 circumaural headphones and rated the loudness, pitch, breathiness, strain and roughness of voice on a 100 mm visual analog scale, with 0 indicating normal voice and 100 indicating severely affected voice. The individual ratings were then compared for inter-rater reliability, factoring in which the final inclusion of the ratings for statistical analyses was done.

To summarize, the retrospective audiological profiles would be compared between the groups, along with voice characteristics, assessed from sustained vowel phonations, recorded using smartphones above specific configuration and analysed using Praat software. This would be followed by perceptual voice analysis using the CAPE-V rating scale by five SLPs. Table 3.2 summarizes the parameters used in the study.

Table 3.2

Summary of parameters used in the study

	Parameter
Audiological Profiling	Pure Tone Audiometry
	Degree and Configuration of Hearing Loss
	Symmetry of Hearing Loss
	Speech Thresholds (SRT/SDT)
	Presence of Cochlear Microphonics
Acoustic Voice Analysis (Praat Software)	Fundamental and Formant Frequencies
	Jitter and Shimmer
	Harmonic-to-noise ratio
Perceptual Voice Analysis (CAPE-V)	Pitch, Loudness, Breathiness, Strain, Roughness, Overall Severity

3.6 Statistical analyses

The data obtained were subjected to statistical analyses using IBM Statistical package social sciences (SPSS) version 25.0 (SPSS Inc., Chicago). Shapiro-Wilk test of normality was done to check for the normal distribution of the data. Multivariate Analysis of Variance (MANOVA) test was carried out for the parametric data, while the Mann-Whitney U test was done to compare the differences (if any) in audiological profiling or vocal characteristics between the groups when the data followed non-normal distribution. The measure of effect size $r = Z/\sqrt{N}$, where Z is the non-parametric statistic, and N is the population size (Berben et al., 2012), was computed for parameters where significant differences were observed in non-parametric tests. Similarly, Partial Eta Squared (η_p^2) was noted wherever significant differences were observed in parametric tests.

Modified Bland-Altman plot and single rater type of interclass correlation (ICC) were also computed to check for the inter-judge agreement (implemented in SPSS) for perceptual ratings. The utility of ICC over Pearson's correlation coefficient as a measure of inter-judge reliability is empirically proven to be reliable for data where the order of the two measurements is unimportant (as in the present study, perceptual ratings of each judge did not follow any temporal order and are made independently of each other) (Berchtold, 2016). Pearson's correlation (r) and Spearman's correlation (ρ) were computed to assess the correlation between categorical and continuous audiological characteristics with voice characteristics. Pearson's correlations were also calculated for acoustic and perceptual voice parameters.

To identify a selected set of the measures (audiological and voice) that most effectively distinguished the onset-based group differences, Fisher Discriminant Analysis (FDA) was done. Each participant's score on the discriminant function was calculated by multiplying the standardized canonical discriminant function coefficient by the test score of each individual on the study measures and summing these products. The error rate in the FDA analysis (indicating the accuracy of classification) was carried out by comparing case wise statistics of participant's discriminant function scores against their original pre-verified condition.

Chapter 4

RESULTS

The present study explored the differences between audiological and voice characteristics between the early and late-onset ANSD groups. The study also analyzed the correlation between the auditory and voice characteristics and tried to predict the variables which can best segregate the groups.

4.1. Audiological Profiling

The audiological profile of 15 individuals (30 ears) with early-onset and 16 individuals (32 ears) with late-onset ANSD who satisfied the inclusionary criteria will be entailed in this section. The profiling of the groups included seven parameters: pure-tone average (PTA), degree of hearing loss, the configuration of hearing loss, symmetry of hearing loss, speech thresholds, speech identification scores and presence of cochlear microphonics.

4.1.1 Pure-Tone Average (PTA) and Degree of Hearing Loss.

The PTA of four frequencies (500, 1000, 2000 and 4000 Hz) was compared for both groups. Using Shapiro Wilk's test, the normality check revealed that PTA data adhered to the normal distribution ($p > 0.05$). Figure 4.1 shows the descriptive statistics of PTA, including the mean (centre line in scatter plot) and the standard deviation (error bars) of both the groups. The mean and the individual PTA thresholds of the early-onset group are relatively higher than the late-onset ANSD group. This observation was verified by an independent sample t-test, which showed that the PTA of the early onset group was significantly higher than the late-onset group [t (60) = 6.12, $p < 0.001$, Cohen's d= 1.91].

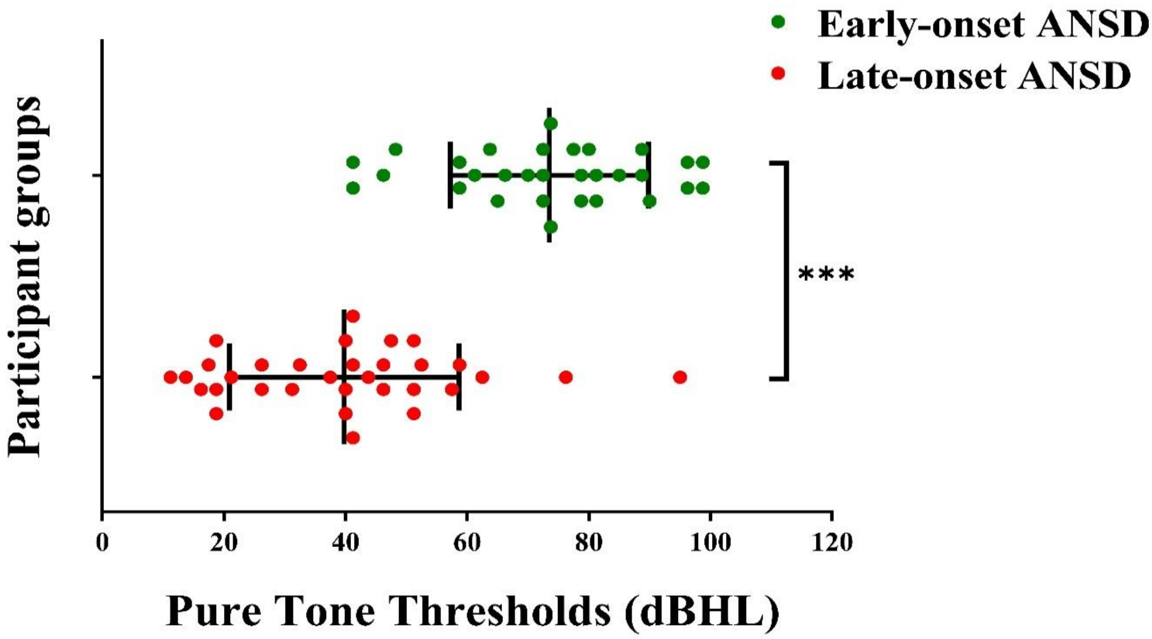

Figure 4.1. Individual data points of PTA of participants of both the groups. The Centre line indicates the mean, and error bars indicate the standard deviation. Plots marked with asterisks indicate the presence of a statistically significant difference (*** p < 0.001).

The proportion of ANSD participants across the different degrees of hearing loss in both groups is depicted in Figure 4.2. The degree-wise distribution of participants revealed that 86.67% of ears (26/30 ears) had a relatively higher degree of hearing loss (moderately severe to a profound degree) in the early-onset group compared to the late-onset group. In contrast to the early-onset group, the proportion of participants with a higher degree of hearing loss was comparatively lesser (5/32 ears accounting for 15.63%) in the late-onset group. Most of the participants in the late-onset group (84.34%, 27/32 ears) exhibited a lesser degree of hearing loss (normal hearing to a moderate degree). The results of the chi-square test also supported the above observations, where a significant association between onset of disorder and degree of hearing loss was seen [χ^2 (6) = 35.16, $p < 0.001$]. On pair-wise comparisons using the test of residuals, it was seen that mild ($p = 0.02$) and severe ($p = 0.01$) degrees of hearing loss had significant group differences, indicative of the utility of degree of hearing loss as an audiological marker for onset-based differences in ANSD. The frequency count of the late-onset group was significantly higher ($p = 0.02$) than the early-onset group in mild hearing loss, while the converse was observed (i.e., the proportion of early-onset being significantly higher than the late-onset, $p = 0.02$) in the severe hearing loss.

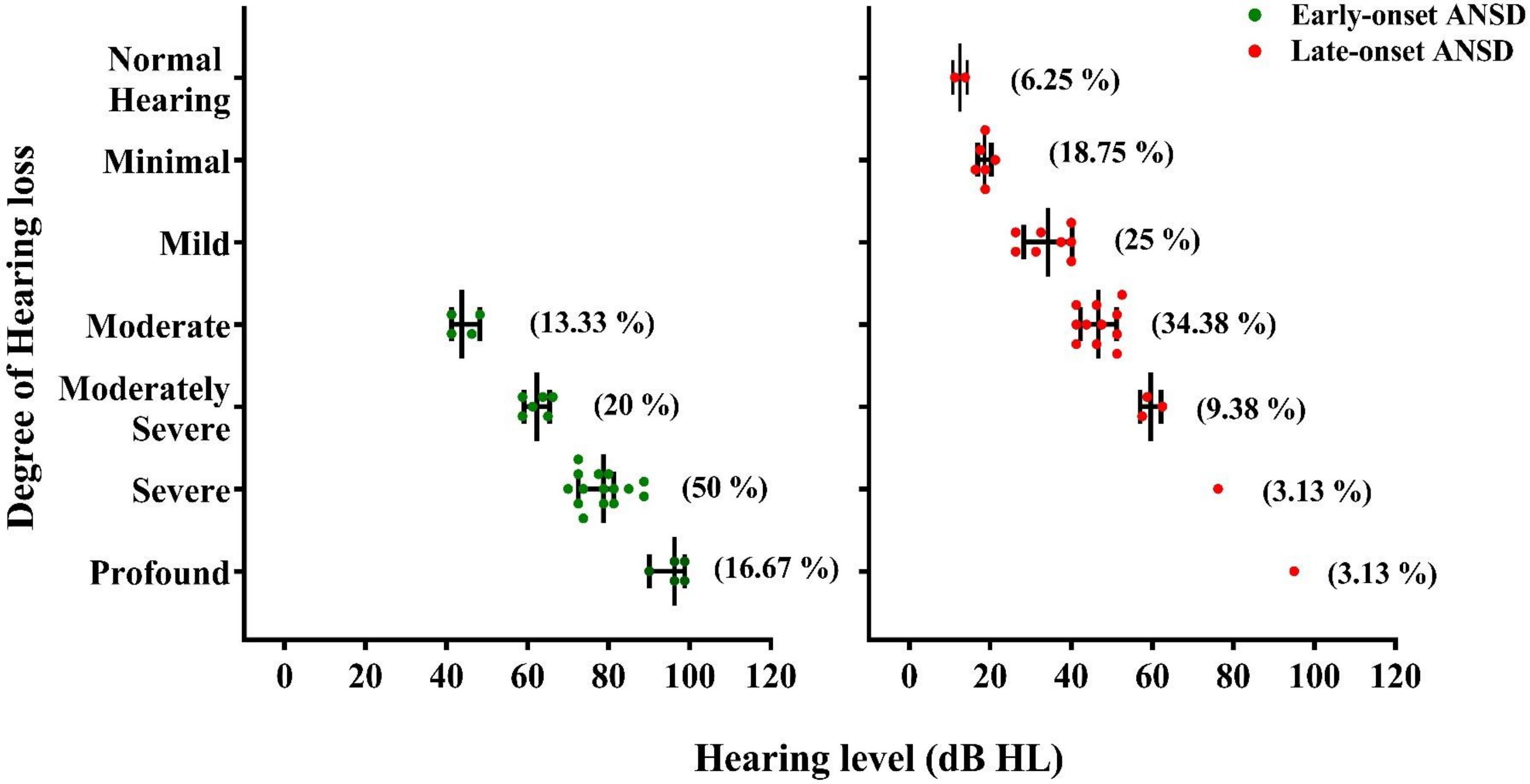

Figure 4.2. Cluster plots showing mean (centre line) and standard deviation (error bars) along with individual (symbols) data for the degree of hearing loss. The numerals on the side of each error bar represent the frequency distribution (in %) of participants for each degree within the group.

4.1.2 Configuration of Hearing Loss

The onset based ANSD groups differed from each other on the configuration of hearing loss, as seen in Figure 4.3. Most of the ears (24/30, 80.00%) exhibited flat configuration followed by sloping configuration (3/30, 10.00%) in the early-onset group, whereas rising configuration (18/32, 56.25%) followed by flat configuration (11/32, 34.38%) were most commonly seen in individuals with late-onset ANSD. On statistical inspection, the Chi-square test revealed a highly significant association of onset of disorder with the configuration of hearing loss [χ^2 (3) = 27.97, $p < 0.001$]. On pair-wise comparisons using the test of residuals, it was seen that flat and rising configurations had significant group differences. The frequency count of the late-onset group was significantly higher (p= 0.003) than the early-onset group in rising configuration, while the converse was observed (i.e., the proportion of early-onset being significantly higher than the late-onset, p= 0.02) in the flat type of configuration.

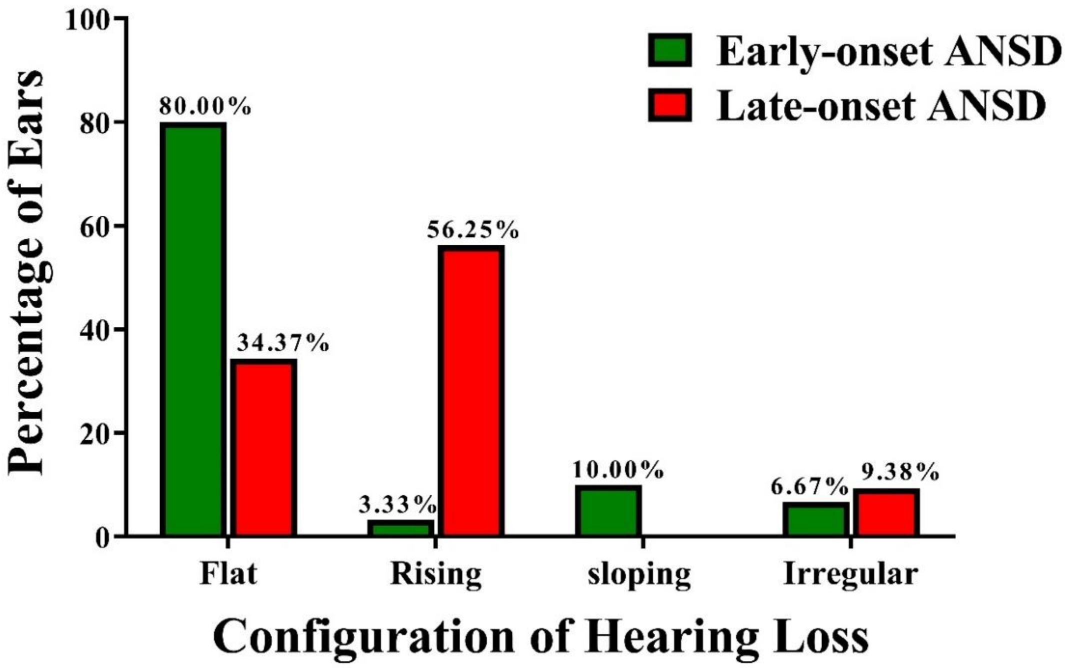

Figure 4.3. Bar graphs representing the percentage of different configurations exhibited by participants of early-onset and late-onset ANSD groups.

4.1.3 Symmetry of Hearing Loss:

Among 31 participants, 19 participants (12/15 in early-onset and 7/16 in late-onset) exhibited binaurally symmetrical thresholds, while the other 12 participants (3/15 in early-onset and 9/16 in late-onset) showed asymmetrical thresholds between the two ears. Figure 4.4 shows the group-wise distribution of symmetry of hearing loss. This was further supported with inferential statistics, where the Chi-square test revealed a significant association of onset of disorder with symmetry of hearing loss [χ^2 (1) = 4.28, p= 0.04]. On pair-wise comparisons using the test of residuals, it was seen that both presence and absence of symmetry had a significant association with onset. The frequency count of the early-onset group was significantly higher (p= 0.04) than the late-onset group in symmetrical hearing loss, while the converse was observed (i.e., the proportion of late-onset being significantly higher than the early-onset, p= 0.04) in the asymmetrical hearing loss.

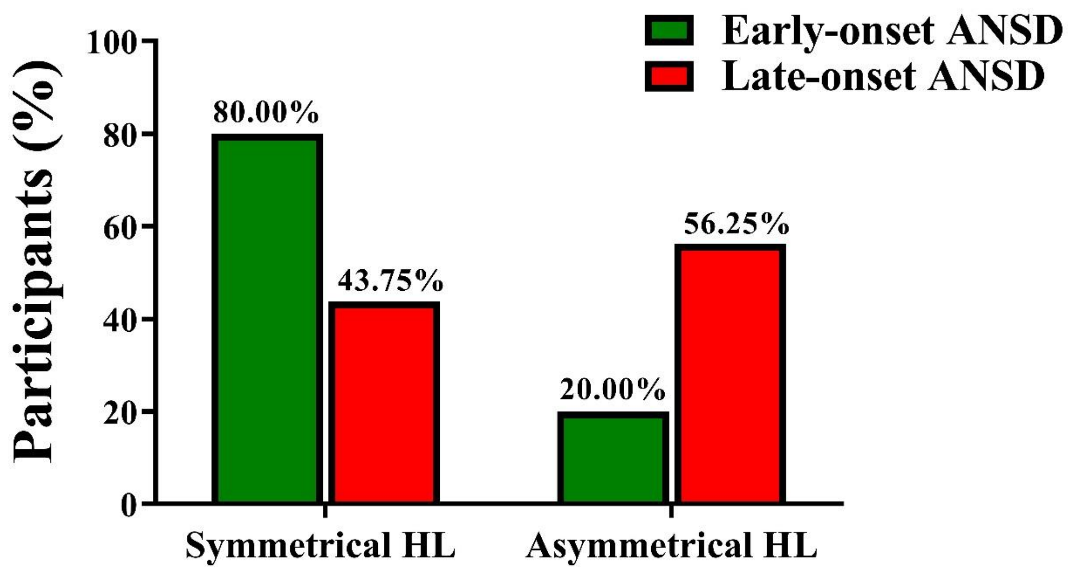

Figure 4.4. Bar graphs representing the presence or absence of symmetrical hearing loss in participants of early-onset and late-onset ANSD groups.

4.1.4 Speech Thresholds

Speech Audiometry results were available for 40 ears (28/32 early and 22/30 late-onset ANSD). Speech Recognition Thresholds (SRT) for bisyllabic words in quiet were available for all late-onset adult participants (22/22 ears), whereas Speech Detection Thresholds (SDT) were available for few early-onset participants (8/28 ears) who were assessed early in life. Owing to modification in the testing strategy and protocol for the pandemic, speech thresholds were not available for few participants. Normality check using the Shapiro Wilks test revealed normal distribution ($p > 0.05$). Figure 4.5 shows the mean of SRT/SDT in dB HL, along with standard deviation for both the groups, indicative of group differences in the speech thresholds. Results of the Independent t-test showed that the SRT/SDT of the early onset group was significantly higher than late-onset group [t (60) = 10.67, $p < 0.001$, Cohen's d = 1.78].

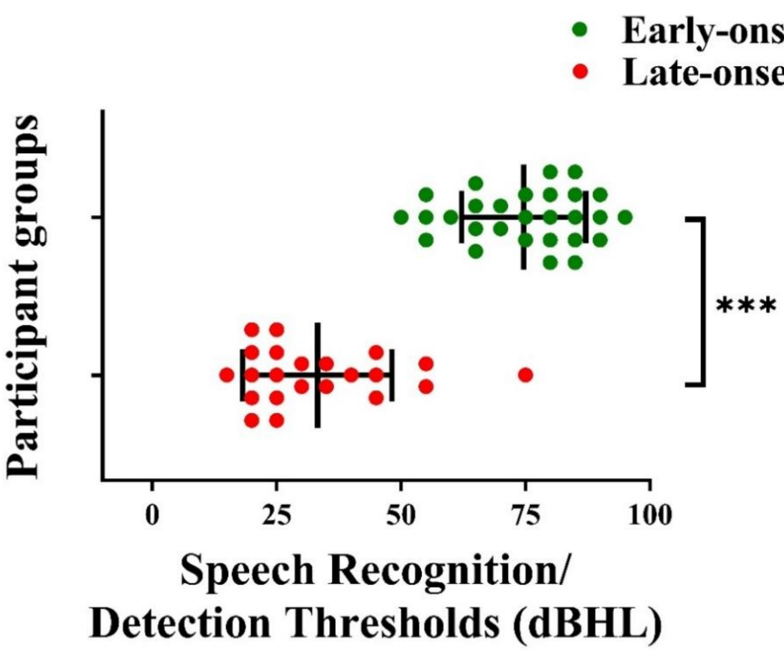

Figure 4.5. Cluster plot denoting median (centre line) and interquartile range (error bars) along with individual SRT/SDT data of participants for both the groups. Plot marked with asterisks indicates the presence of statistically significant difference (*** - $p < 0.001$).

4.1.5 Cochlear Microphonics (CM)

Out of 62 ears, only 25 ears [8/32 (25.00%) in late and 13/30 (56.65%) in early-onset] had Cochlear Microphonics (CM) present. Group differences in the distribution of CM (absence or presence) of CM can be seen in Figure 4.6. Inferential Statistics (Chi-square test) revealed no significant association between onset of disorder and presence of CM loss [χ^2 (1) = 2.48, p = 0.12].

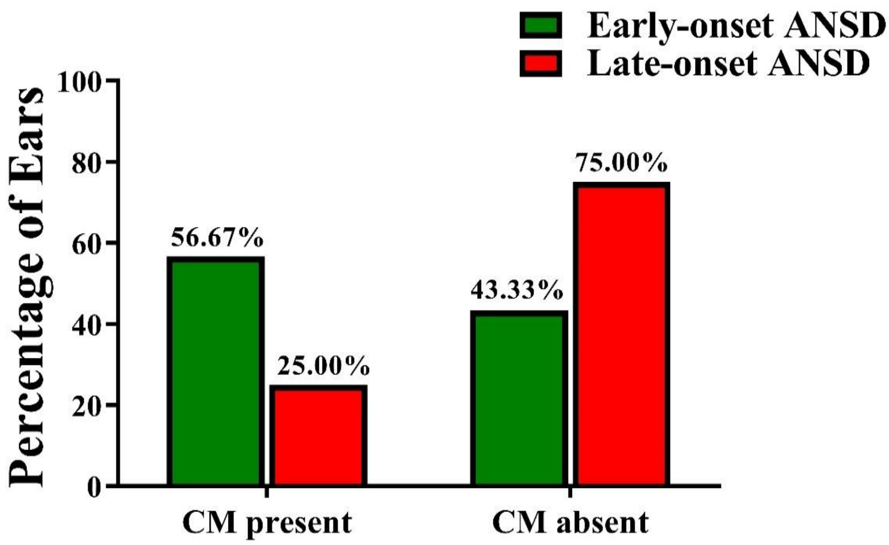

Figure 4.6. Bar graphs representing the presence or absence of cochlear microphonics in participants of early-onset and late-onset ANSD groups.

4.2 Voice Characteristics

Although the voice samples were obtained from 31 participants, three samples were excluded due to background noise (> 60 dB SPL). Hence, the vocal characteristics from the recorded waveforms with clear waveforms were analyzed. This comprised 12 individuals with early-onset and 16 individuals with late-onset. Acoustic parameters of voice were assessed using Praat software, where fundamental and formant frequencies, jitter, shimmer and the harmonic-to-noise ratio was computed and compared between the groups. A similar comparison was made for perceptual voice analysis using a visual analog rating scale, and parameters such as pitch, loudness, breathiness, strain and roughness were rated perceptually. The statistical differences in the voice characteristics on the acoustic and perceptual parameters are highlighted in this section.

4.2.1 Group Differences in Acoustical Parameters of Voice.

Fundamental frequency and formant frequencies. Shapiro-Wilk test showed the acoustical data (fundamental and formant frequencies) of all the vowels (/a/, /i/ & /u/) adhered to normal distribution ($p > 0.05$). The descriptive statistics comprising the mean of fundamental and formant frequencies and standard deviation for the three vowels are shown in Figure 4.7. The results of inferential statistics (multivariate analysis of variance, MANOVA) for the significant group differences are marked by asterisks in the same figure. On visual examination, the late-onset ANSD group, in general, exhibited higher formant frequencies compared to the early-onset group.

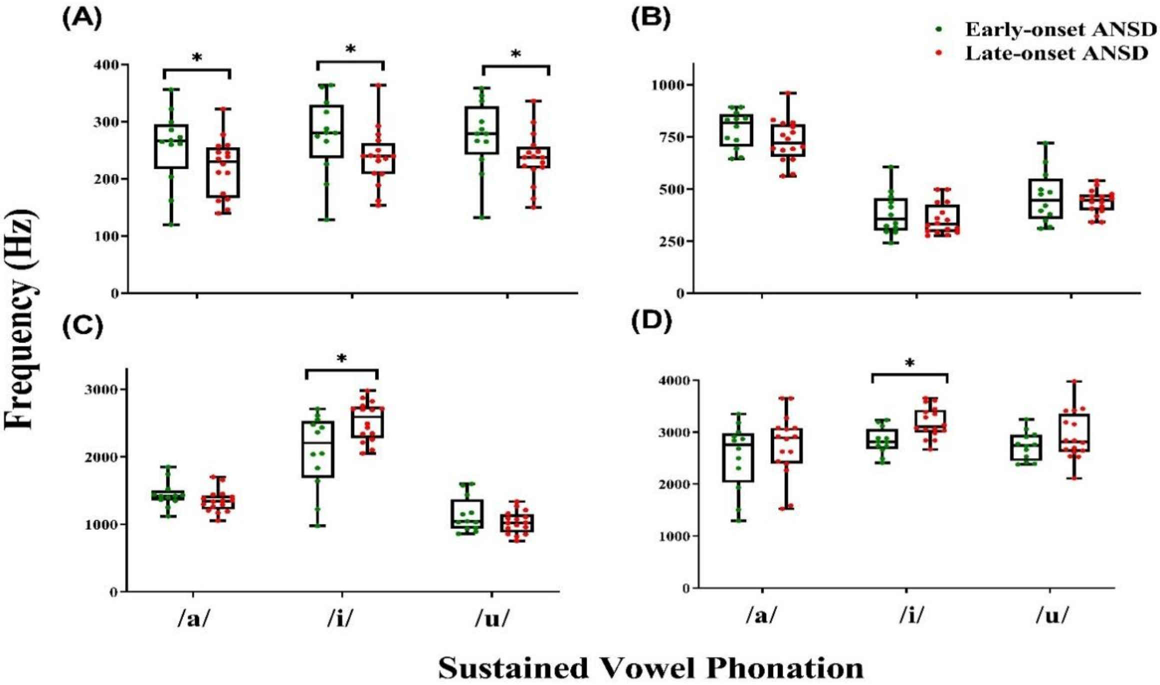

Figure 4.7 Box plots depicting median (center line), along with interquartile range (error bars) of (A) Fundamental frequency F_0, (B) first formant: F_1, (C) second formant: F_2 and (D) third formant: F_3 of three sustained vowel phonations (/a/, /i/, /u/) for early-onset and late-onset ANSD groups. The individual data points for the f_0 and the first three formants are also indicated on the corresponding plots. Graphs marked with asterisks indicate the presence of a statistically significant difference (* - $p < 0.05$).

The results of MANOVA for vocal pitch analyses showed the main effect of ANSD onset for fundamental frequencies of all three vowels, as shown in Table 4.1. The results showed that the f_0 of early-onset group was significantly higher (/a/: p = 0.03 /i/: p = 0.02, /u/: p = 0.02) than late-onset for all the vowels reported in the study. Additionally, the main effect of ANSD onset was also seen for second and third formants (F_2 & F_3) of vowel /i/, with the late-onset group demonstrating significantly higher F_2 (p = 0.02) and F_3 (p = 0.01) compared to the early-onset group. The effect size for the acoustic parameters where significant differences were seen was in the range of 0.16 to 0.24, indicative of a small effect size.

Table 4.1.

Results of MANOVA showing the main effect of onset on fundamental and formant frequencies of sustained phonations of vowels (/a/, /i/ and /u/). Highlighted frames represent parameters with the significant main effect of the group.

Acoustic Frequency parameters	***Vowels***		
	/a/	*/i/*	*/u/*
Fo	F (1,26) = 4.96, p = 0.03, $ŋ_p^2$= 0.16	F (1,26) = 5.96, p = 0.02, $ŋ_p^2$= 0.19	F (1,26) = 6.35, p = 0.02, $ŋ_p^2$= 0.20
F1	F (1,26) = 3.79 p = 0.06, $ŋ_p^2$= 0.13	F (1, 26) = 1.89, p = 0.44, $ŋ_p^2$= 0.07	F (1, 26) = 0.27, p = 0.61, $ŋ_p^2$= 0.01
F2	F (1, 26) = 1.92, p = 0.18, $ŋ_p^2$= 0.07	F (1,26) = 6.10, p = 0.02, $ŋ_p^2$= 0.20	F (1, 26) = 1.89, p = 0.18, $ŋ_p^2$= 0.07
F3	F (1, 26) = 0.80, p = 0.38, $ŋ_p^2$= 0.08	F (1,26) = 8.02, p = 0.01, $ŋ_p^2$= 0.24	F (1, 26) = 1.06, p = 0.31, $ŋ_p^2$= 0.04

The parameters in which onset-based group differences are significantly seen (F_0 of each of the three vowels and the formants F_2 and F_3 of /i/) for phonation samples obtained from two female participants (one each belonging to the different onset group) is shown in Figure 4.8 (for F_0) and 4.9 (for F_2 & F_3 of /i/) respectively. The onset-based differences are visually appreciable in their spectrograms, as indicated in Figure 4.8 (for F_0) and 4.9 (for F_2 & F_3 of /i/), respectively. The colour-coded bands in the spectrogram correspond to bands of acoustic energy. On visual inspection, it is clear that F_0 is distantly located for two groups (Figure 4.8). It is also seen that the energy bands depicting the portions of F_2 and F_3 are located differently for the two samples

(Figure 4.9). Further, the mean F_2 and F_3 for the early-onset group was 2108 and 2875 Hz, respectively, whereas the same was higher (2529 Hz and 3187 Hz) for the late-onset group. However, no statistical differences were observed in the first formant of vowel /i/.

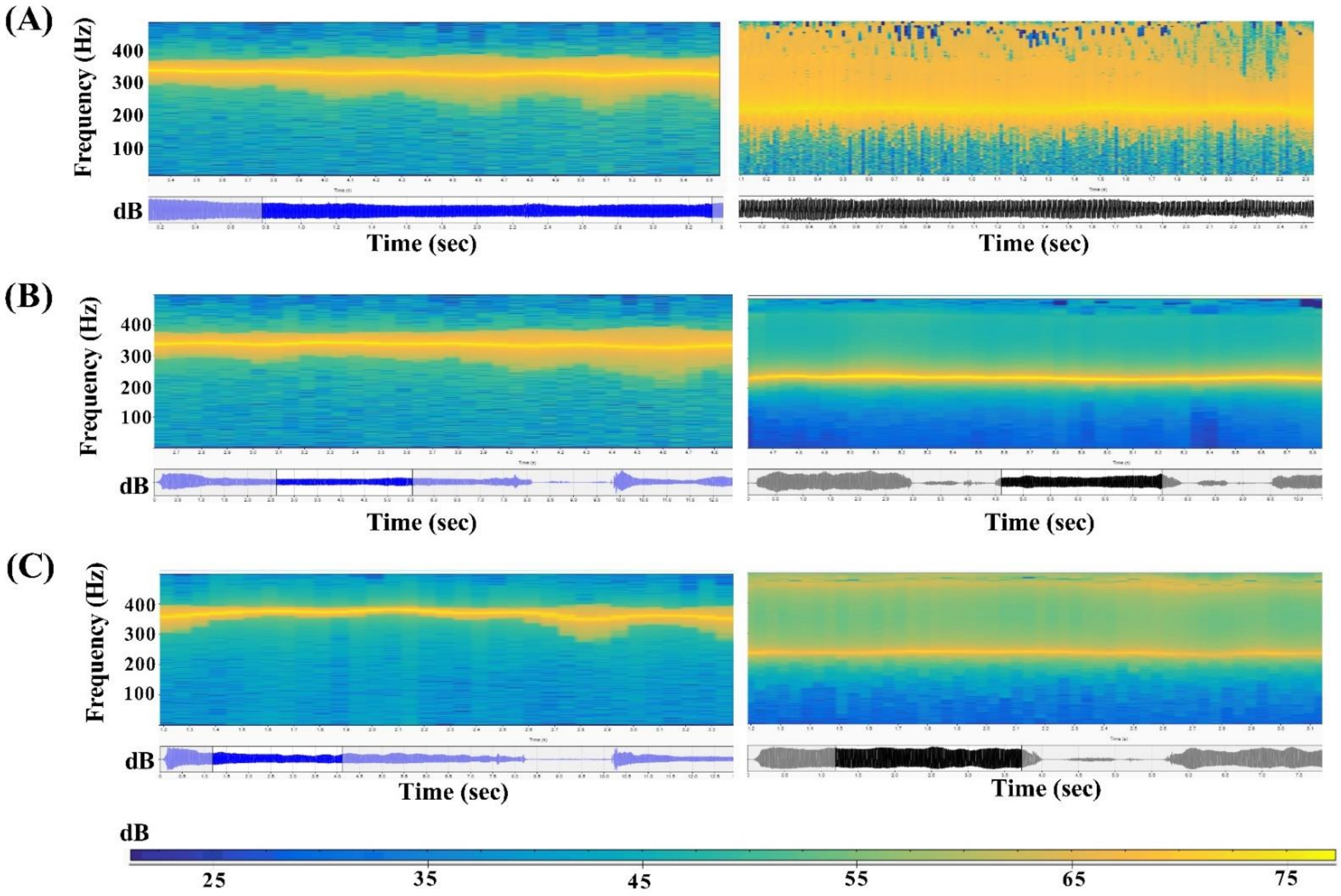

Figure 4.8. Spectrograms of (A) /a/, (B) /i/ and (C) /u/ sustained phonation (for F_0 differences) of a female patient of early-onset (blue, left) and late-onset (black, right) ANSD.

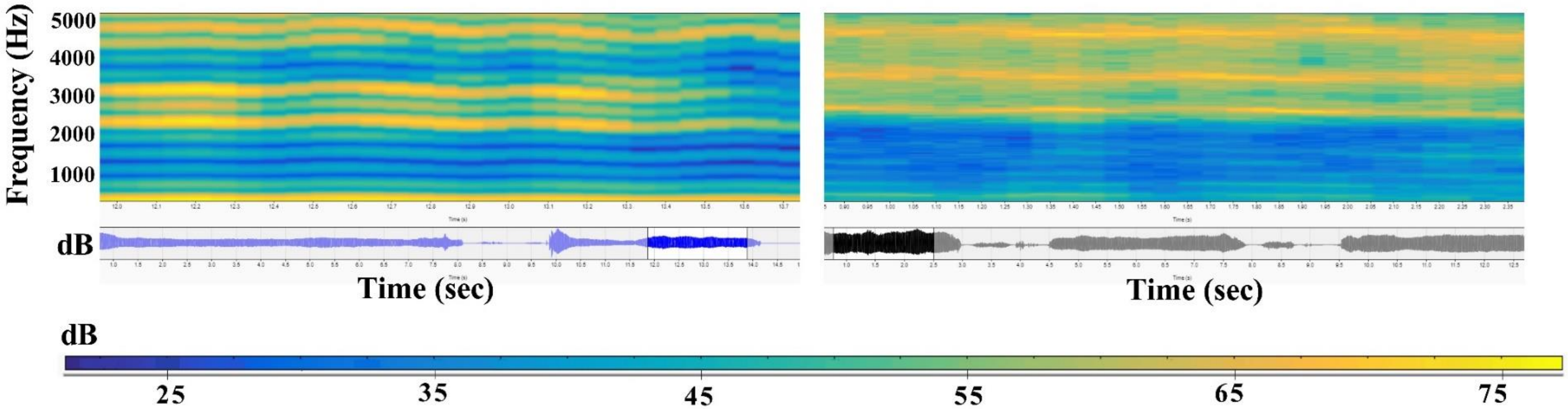

Figure 4.9: Spectrograms of /i/ sustained phonation (for F_2 and F_3 differences) of a female patient of early-onset (blue, left) and late-onset (black, right) ANSD.

Perturbations and Harmonic-to-noise ratio (HNR). Shapiro-Wilk test revealed non-normal distribution for perturbations (frequency perturbation: jitter; and amplitude worry: shimmer) of all three vowels ($p < 0.05$), while the data corresponding to the harmonic-to-noise ratio (HNR) was normally distributed ($p > 0.05$). The median values (centre line) and the interquartile range (errors bars) of these three measures are shown in Figure 4.10. The early-onset group had higher frequency and amplitude perturbations for all the sustained phonation. On the other hand, a relatively lower HNR was recorded in the voice samples of the early-onset group, especially for /a/ phonation. However, none of the above-cited differences withstood the statistical verification, as shown in Table 4.2.

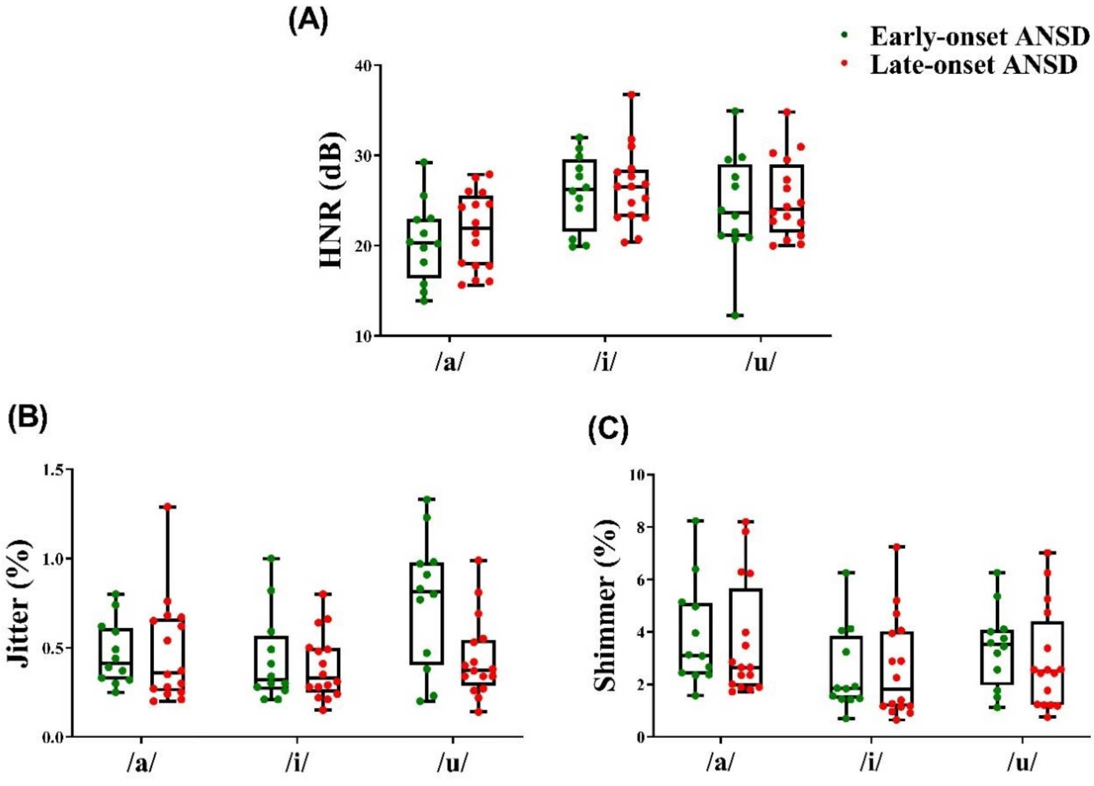

Figure 4.10. Box plots depicting median (centre line), along with interquartile range (error bars) for (A) Harmonic-to-Noise ratio (HNR), (B) Frequency perturbation (Jitter) and (C) perturbations (Jitter and Shimmer, respectively) of all three sustained vowel phonations of early-onset and late-onset ANSD groups.

Table 4.2.

Results of inferential statistical test (Mann-Whitney U and Independent t-test) for comparison of group differences in measures of signal to noise ratio (HNR) and perturbations (jitter, shimmer) in the voice.

Acoustic Parameter		**Test statistic /z/ or *t***	***p***
HNR	**/a/**	t (26) = -0.64	0.53
	/i/	t (26) = 0.17	0.86
	/u/	t (26) = -1.08	0.29
Jitter	**/a/**	/z/= 1.21	0.22
	/i/	/z/= 0.33	0.74
	/u/	/z/= 1.86	0.06
Shimmer	**/a/**	/z/= 0.84	0.40
	/i/	/z/= 0.19	0.85
	/u/	/z/= 1.67	0.10

4.2.2. Group Differences in Perceptual Parameters of Voice Quality

The inter-judge reliability of perceptual ratings on voice analyzed using the modified Bland Altman plot is shown in Figure 4.11. The average perceptual agreement scores of all five speech-language pathologists (SLPs) is shown on the x-axis, and the difference in perceptual agreement score is shown on the y-axis. On visual inspection of the Bland Altman plot, it is apparent that maximum perceptual judgements (262 out of 280) of the SLPs were within the limits of agreement (± 1.96 SD, blue shaded area in Figure 4.11). The analyses of the outliers in the modified Bland Altman plot showed that 18 out of 260 judgements did not correlate well, accounting for an error of 6.43%. The overall percentage of agreement between judges was approximately 93.57%, indicative of high inter-judge reliability ratings.

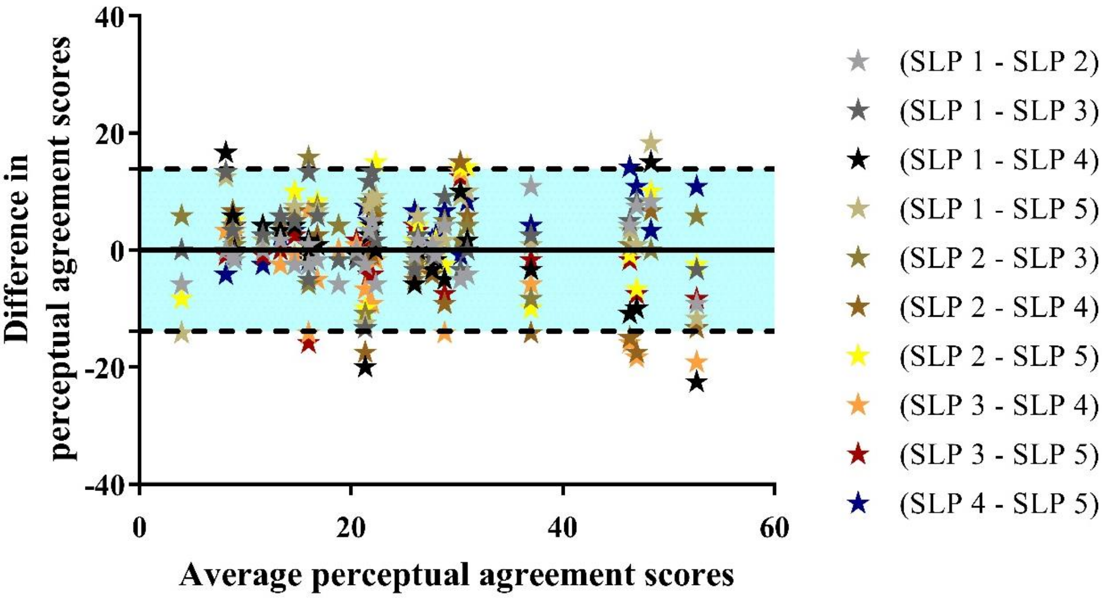

Figure 4.11. Bland-Altman Plots for Inter-judge agreement. Stars of different colours show the agreement between 2 judges. The blue shaded area represents the limits of agreement (± 1.96 SD) of the observations.

These observations were further complemented by the results of interclass correlation (ICC) analyses which revealed a moderate to high degree of agreement amongst the perceptual judgements of the five SLPs, as shown in Table 4.3.

Table 4.3.

Objective measure of agreement (mean and range of interclass correlation - ICC coefficients) in the perceptual judgements of the five speech-language pathologists (SLPs).

Parameter	**Average ICC coefficient**	**Range of ICC coefficient**	***p* value**
Pitch	0.67	0.47 – 0.78	< 0.001
Loudness	0.59	0.43 – 0.75	< 0.001
Strain	0.82	0.72 – 0.90	< 0.001
Roughness	0.71	0.57 – 0.83	< 0.001
Breathiness	0.69	0.54 – 0.81	< 0.001
Overall Severity	0.88	0.80 – 0.99	< 0.001

Shapiro-Wilk test revealed normality ($p > 0.05$) in average perceptual ratings of on pitch, loudness, strain, breathiness and roughness. The descriptive statistics with mean scores, along with standard deviation, of perceptual rating are shown in Figure 4.12, with the SLPs rating for early-onset group being more affected (greater pitch, breathiness, strain and roughness) than late-onset group. The perceptual parameters with significant statistical difference (MANOVA test) are marked with asterisks in the same figure. MANOVA revealed the main effect of ANSD onset on all perceptual vocal parameters [pitch: $F(1,26) = 7.77$, $p = 0.01$, $ŋ_p^2 = 0.23$, breathiness: $F(1,26) = 5.68$, $p = 0.03$, $ŋ_p^2 = 0.18$; roughness: $F(1,26) = 9.24$, $p = 0.01$, $ŋ_p^2 = 0.22$; strain: $F(1,26) = 7.29$, $p = 0.01$, $ŋ_p^2 = 0.22$; and overall severity: $F(1,26) = 4.77$, $p = 0.04$, $ŋ_p^2 = 0.16$] but one parameter [Loudness: $F(1,26) = 1.05$, $p = 0.31$, $ŋ_p^2 = 0.04$].

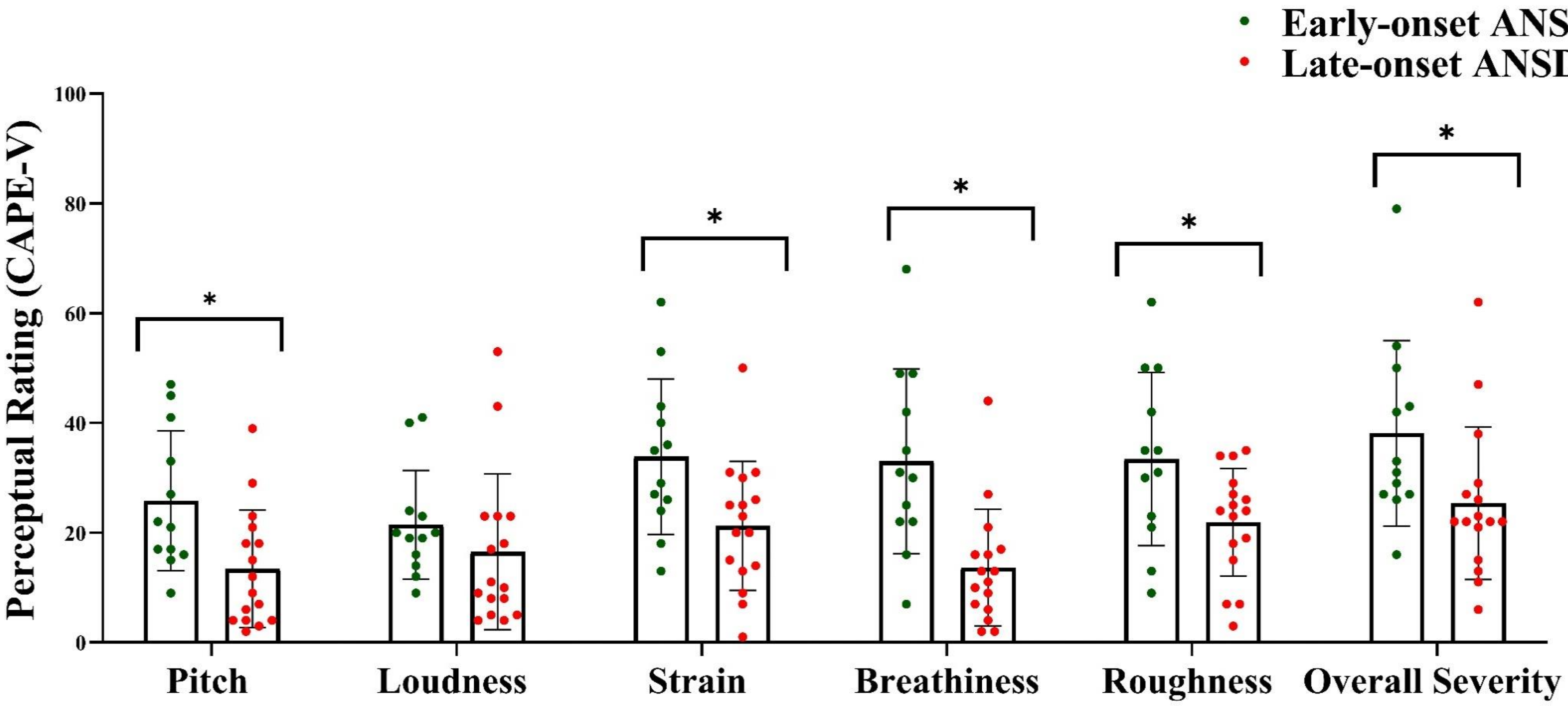

Figure 4.12. Bar Graphs depicting the means, along with standard deviation (error bars), of perceptual rating of voice quality based on five parameters in early-onset and late-onset ANSD groups. Plots marked with asterisks indicate the presence of a statistically significant difference (* $p < 0.05$).

4.3 Correlation between audiological characteristics and vocal parameters

The acoustic and perceptual voice parameters were correlated with scalar quantities (numerical values) in audiological measures using the Pearson correlation coefficient. Pure-tone average thresholds had mild to moderate correlation with F_2 of /u/, jitter of /a/, breathiness and roughness. Speech thresholds also showed mild to moderate correlation with F_2 of /u/ and roughness. Similarly, the categorical audiological characteristics (degree, configuration, symmetry and presence of cochlear microphonic) were correlated with vocal parameters using the Spearman correlation coefficient. The correlation coefficient for both scalar and categorical quantities (enlisted above), which reached statistical significance, are shown in Table 4.4.

The correlation between acoustic and perceptual parameters of voice revealed mild to moderate positive correlation of F_2 of /u/ with pitch ($r = 0.50$, $p = 0.01$), breathiness ($r = 0.49$, $p = 0.03$), strain ($r = 0.46$, $p = 0.01$), roughness ($r = 0.37$, $p = 0.04$) and overall severity ($r = 0.43$, $p = 0.02$).

Table 4.4.

Significant correlations (Pearson's: r and Spearman's: ρ) *between audiological characteristics and vocal parameters, along with p value, denote a significant correlation between the two variables. The other parameters where the correlations were not reaching statistical significance were not shown in the table to improve readability.*

Audiological Characteristic	***Vocal Parameter***	***Correlation Coefficient***	***p***
PTA	F_2 /u/	r = 0.38	0.03
	Jitter /a/	r = 0.39	0.04
	Breathiness	r = 0.38	0.04
	Roughness	r = 0.39	0.04
SRT/SDT	F_0 /u/	r = -0.48	0.02
	Jitter /u/	r = 0.52	0.02
Degree	F_2 /a/	ρ = 0.38	0.04
	Jitter /a/	ρ = 0.40	0.03
Configuration	Jitter /u/	ρ = 0.57	0.002
Symmetry	F_2 /a/	ρ = -0.41	0.03
	Jitter /a/	ρ =- 0.54	0.003
	Jitter /i/	ρ = -0.41	0.03
	Shimmer /a/	ρ = -0.42	0.03
	HNR /a/	ρ = -0.48	0.01
	Roughness	ρ = -0.44	0.02
Presence of CM	Jitter /i/	ρ = 0.47	0.01
	Shimmer /i/	ρ = 0.40	0.04
	HNR /a/	ρ = -0.46	0.01
	HNR /i/	ρ = -0.44	0.02

Note: PTA: Pure Tone Average, SRT: Speech Recognition thresholds, SDT: speech Detection Thresholds, CM: Cochlear Microphonics, HNR: Harmonic-to-Noise Ratio

4.4 Discriminant Analysis Identifying the best metric of group differences

To identify a selected set of the measures (audiological and voice) that most effectively distinguished the onset-based group differences, Fisher discriminant analysis was done. For the audiological data, better ear thresholds were used, assuming that vocal characteristics correlate to the better ear's audiological characteristics. The canonical discriminant function (DF), which statistically clustered behavioural measures that segregated ANSD groups, accounted for 100 % of the variance (Wilks's lambda, λ (14) = 0.046, $\chi 2 = 44.66$, $p < 0.001$).

However, an examination of the weights for each test indicated that three audiological characteristics (PTA, degree and configuration), one acoustic vocal parameter (F_0 of /i/ and /u/), along with one perceptual vocal parameter (overall severity rating), were heavily weighed (canonical coefficients) on DF as reflected in Table 4.5. The corresponding structure matrix is also shown in the same table. The structure matrix indicates the pooled within-group correlations between discriminating variables and standardized canonical DF. The canonical DF obtained in the study based on the weights (Table 4.5) is summarized below:

DF1: (3.09 × PTA) – (3.81 × Degree) + (1.23 × Configuration) – (2.47 × Fo of /i/) + (2.12 × Fo of /u/) + (1.39 × Overall severity rating)

Table 4.5.

Contribution (weights) of auditory tests for group membership prediction of onset based ANSD groups (Note: Variables are ordered by the absolute size of correlation within the function - largest absolute correlation between each variable and any discriminant function)

Discriminating Variable/ Tests	***Weights***	***Structure matrix***
Degree	-3.81	-0.43
PTA	3.09	-0.40
Configuration	1.23	-0.78
Fo /i/	-2.47	-0.11
Fo /u/	2.12	-0.11
Overall Severity Rating	1.39	-0.07

Each participant's score on the discriminant function was calculated by multiplying the standardized canonical DF coefficient by the test score of each individual on the study measures and summing these products. Thus, the calculated frequency (y-axis) for each discriminant score (x-axis) is shown in Figure 4.13. It is clear from the figure that the DF separates the early-onset ANSD from the late-onset ANSD group, which emerged as two distinct clusters that are concentrated on either side of the reference line.

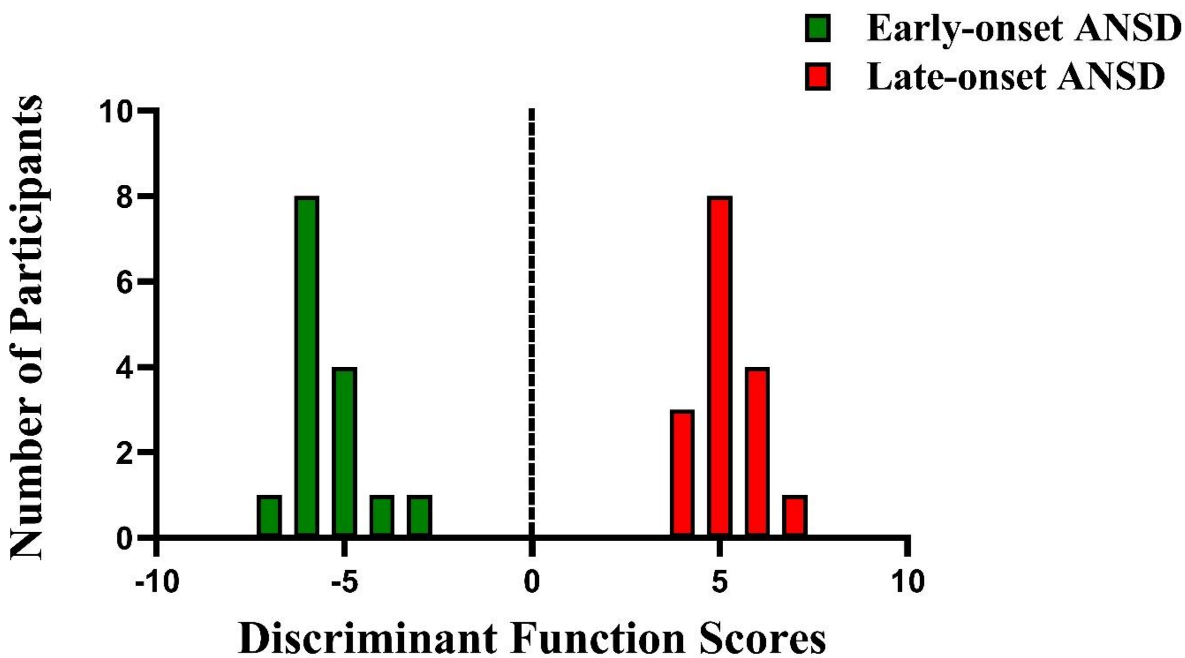

Figure 4.13. Bar graphs representing the Discriminant Function scores for the segregation of both groups. The dotted line is the reference for cut-off scores between the groups on the discriminant function.

The error rate in the FDA analysis (indicating the accuracy of classification) was carried out by comparing case wise statistics of participant's DF scores against their original pre-verified condition, as shown in Table 4.6. An overall 100.00% accuracy in the classification was seen, indicative of the clear segregation of the groups based on the weights obtained in the FDA.

Table 4.6.

Accuracy of discriminant function analyses comparing predicted and original group memberships. Total participants (number count) are tabulated with the corresponding percentage in parentheses

	Predicted Group Membership		
Original Group	Early-onset	Late-onset	Total
Early-onset	100 % (15)	0%	100 % (15)
Late-onset	0%	100 % (16)	100 % (16)
Total	100 % (15)	100 % (16)	100 % (31)

To summarize, early and late-onset ANSD groups are significantly different in terms of PTA, degree, speech thresholds, configuration and symmetry of hearing loss. Apart from this, they are also different in voice parameters, such as fundamental frequencies of all the vowels assessed and formants (F_2 and F_3) of /i/. The significant differences were also seen in perceptual voice evaluation, where the severity of pitch, strain, breathiness, roughness and overall severity was rated greater for the early-onset group. Further, the audiological characteristics were in correlation with some acoustic and perceptual parameters. Among the audiological characteristics, PTA, degree and configuration of hearing loss were the most sensitive metrics for group categorization, while acoustic parameters (Fo of /i/ and /u/) and perceptual (overall severity rating) in voice also served as highly discriminable characteristics between the ANSD onset-based group classification. The effect of ANSD onset on each measure audiological and vocal parameters are summarized in Table 4.7, indicative of robust sensitivity (based on effect size) of the audiological measures over voice measures in identifying onset-based group differences.

Table 4.7.

Effect of ANSD onset on audiological and vocal parameters considered in the study. Highlighted frames represent parameters with the significant main effect of the group.

Measure	*Effect of group*	*Early-onset vs late-onset*	*Sensitivity (Effect size)*	*Significance (p)*
Audiological Characteristics				
PTA	t (60) = 6.12	EO> LO	Cohen's d = 1.91	$p < 0.001$***
Degree of Hearing Loss	χ^2 (6) = 35.16	Mild: EO< LO Severe: EO> LO	-	$p < 0.001$***
Configuration	χ^2 (3) = 27.97	Flat: EO> LO Rising: EO< LO	-	$p < 0.001$***
SRT/SDT	t (60) = 10.67	EO> LO	Cohen's d = 1.78	$p < 0.001$***
Presence of CM	χ^2 (1) = 2.48	EO> LO	-	p=0.12
Symmetrical Hearing loss	χ^2 (1) = 4.28	EO> LO	-	p= 0.04*
Vocal Characteristics (acoustical)				
F0 /a/	F (1,26) = 4.96	EO> LO	η_p^2= 0.16	p = 0.03*
F0 /i/	F (1,26) = 5.96	EO> LO	η_p^2= 0.19	p = 0.02*
F0 /u/	F (1,26) = 6.35	EO> LO	η_p^2= 0.20	p = 0.02*
F1 /a/	F (1,26) = 3.79	EO= LO	η_p^2= 0.13	p = 0.06,
F1 /i/	F (1, 26) = 1.89	EO= LO	η_p^2= 0.07	p = 0.44
F1 /u/	F (1, 26) = 0.27	EO= LO	η_p^2= 0.01	p = 0.61
F2 /a/	F (1, 26) = 1.92	EO= LO	η_p^2= 0.07	p = 0.18
F2 /i/	F (1,26) = 6.10	EO< LO	η_p^2= 0.20	p = 0.02*
F2 /u/	F (1, 26) = 1.89	EO= LO	η_p^2= 0.07	p = 0.18
F3 /a/	F (1, 26) = 0.80,	EO= LO	η_p^2= 0.08	p = 0.38
F3 /i/	F (1,26) = 8.02	EO< LO	η_p^2= 0.24	p = 0.01*

F3 /u/	F (1, 26) = 1.06	EO= LO	$ŋ_p^2$= 0.04	*p* = 0.31
HNR /a/	t (26) = -0.64	EO= LO	-	*p*= 0.53
HNR /i/	t (26) = 0.17	EO= LO	-	*p*= 0.86
HNR /u/	t (26) = -1.08	EO= LO	-	*p*= 0.29
Jitter /a/	/z/= 1.21	EO= LO	-	*p*= 0.22
Jitter /i/	/z/= 0.33	EO= LO	-	*p*= 0.74
Jitter /u/	/z/= 1.86	EO= LO	-	*p*= 0.06
Shimmer /a/	/z/= 0.84	EO= LO	-	*p*= 0.40
Shimmer /i/	/z/= 0.19	EO= LO	-	*p*= 0.85
Shimmer /u/	/z/= 1.67	EO= LO	-	*p*= 0.10
Vocal Characteristics (perceptual)				
Pitch	F (1,26) = 7.77	EO> LO	$ŋ_p^2$= 0.23	*p* = 0.01*
Loudness	F (1,26) =1.05	EO= LO	$ŋ_p^2$= 0.04	*p* = 0.31
Strain	F (1,26) = 7.29	EO> LO	$ŋ_p^2$= 0.22	*p* = 0.01*
Breathiness	F (1,26) = 5.68	EO> LO	$ŋ_p^2$= 0.18	*p* = 0.03*
Roughness	F (1,26) = 9.24	EO> LO	$ŋ_p^2$= 0.22	*p* = 0.01*
Overall Severity	F (1,26) = 4.77	EO> LO	$ŋ_p^2$= 0.16	*p* = 0.04*

Note: ***- significance at the level of 0.001; *- significance at the level of 0.05

Chapter 5

DISCUSSION

The research aimed to describe the differences in audiological profiling and vocal characteristics of early and late-onset ANSD using auditory tests and vocal measures (acoustical and perceptual). The findings of the study point at key indicators in the vocal characteristics that can segregate the two onset based ANSD groups (figures 4.11 & 4.7). Amongst the few available retrospective studies, the existence of late-onset ANSD is documented in case studies by only a few researchers (Berlin et al., 2010; De Siati et al., 2020; Jijo & Yathiraj, 2012; Kumar & Jayaram, 2006; Narne et al., 2014; Norrix & Velenovsky, 2014). Thus, the findings from the current study are the first of its kind in research design, which plausibly explains the onset-based group differences in vocal characteristics in a prospective control group design.

Although the data collection was started during the pandemic, the strength of the study is the precise control of variables at the start of the study. The study participants were age and gender-matched between the groups to reduce the effect of these confounding variables. All the subjects passed language screening in the late-onset ANSD group, which helped the experimenter understand the aptness of the participant inclusion, as the presence of early ANSD (even if of milder degree) is known to adversely affect language outcomes (Rance & Barker, 2009). The control was also exercised on recording voice samples, with prior succinct segregation of environmental noise using mobile applications. The check between android based voice recording and the conventional voice recording using the Computerized Speech Lab (CSL) application during the pilot is another strength of the study. The combination of these experiment-based control further consolidates the results obtained in the study, apart from providing flexibility to conduct such studies during the COVID -19 pandemic. These strengths increase the scope of validating the findings of the study.

5.1 Effect of ANSD onset on non-auditory characteristics

There was a strong gender bias seen in the disorder, with more females being affected than males (2.44:1). This finding is on par with the earlier reported gender differences in auditory neuropathy spectrum disorder (Kumar & Jayaram, 2006; Prabhu & Jamuar, 2017). This is attributed to more influence of hormones and their abnormal changes in female participants. To reduce the confounding effect of the variable, a similar number of males and females were taken in both groups, which adds to the strength of the article.

All the participants taken in the study had ANSD affecting both ears. This was in accordance to the laterality reported in previous studies (Berlin et al., 2010; Narne et al., 2014). However, few studies report the existence of unilateral ANSD (Konrádsson, 1996; Podwall et al., 2002), but the prevalence of the same was found to be minimal in these studies. Berlin et al. (2010) reported 93% of their cases to be bilaterally affected. Though all the participants had bilateral ANSD, the chances of hearing loss being symmetrical were different in both groups. The Early-onset group had more chances of symmetrical hearing loss (80%, figure 4.3) than the late-onset ANSD. This could be due to the progression of the disorder in early-onset cases, gradually leading to more severe hearing loss in both ears and presentation of that as symmetrical hearing loss.

The etiology of the early-onset ANSD group was reported to be hyperbilirubinemia, hypoxia and high post-natal fever, whereas it was reported to be either idiopathic or exposure to high levels of noise in the late-onset ANSD group. Most of the cases in the early-onset group did not report any high risk during the natal or post-natal duration, which could have possibly led to cause ANSD. This can be attributed to more homebirths in the Indian scenario (Gares et al., 2012), which eventually have led to a lack of awareness of high risks at the time of birth and during the postnatal period.

The mean age of onset in early-onset group was reported to be 6.23 years whereas for the late-onset group it was seen to be 18.51 years. The variability in onset can be seen in previous literature where earlier western researches (Berlin et al., 2010; Rance et al., 1999) had found the onset to be before the adolescence, whereas later Indian and few western researchers (De Siati et al., 2020; Jijo & Yathiraj, 2012; Kumar & Jayaram, 2006; Narne et al., 2014; Prabhu et al., 2012) have shown the onset to be during or post adolescent period. This variation in onset is attributed to the variable etiology.

5.2 Effect of ANSD onset on auditory characteristics

The findings from the study showed that participants with early-onset ANSD showed higher pure-tone average thresholds and a higher degree of hearing loss than the late-onset group (figure 4.1 & 4.2). Better pure-tone thresholds and a lesser degree of hearing loss (mild to moderate degree) noted in the late-onset ANSD group can be an indication of compromised neural functioning in the presence of preserved inner hair cell (IHC) functioning (Starr et al., 2008). The delayed onset could have spared the functional inner hair cells, which primarily relay the sound to the auditory nerve. This is reflected in its clinical correlate, i.e., better auditory thresholds. On the other hand, the site of lesion in early-onset ANSD groups is most probably the inner hair cell loss, reflected in the pure tone audiometry as severe to profound hearing loss (Amatuzzi et al., 2011). Thus, these findings highlight the possibility of neuronal impairment in the late-onset group while the early onset groups predominantly have overall IHC damage, along with neuronal impairment (Kujawa & Liberman, 2015; Moser & Starr, 2016). These findings were consistent with speech thresholds, where the speech recognition threshold/ speech detection thresholds were less than 50 dBHL for all late-onset participants and more than 50 dBHL for all early-onset participants (figure 4.5). The PTA was highly correlated with the speech thresholds. Thus, speech recognition/ detection followed the same trend as pure-tone audiometry in these individuals.

The configuration of hearing loss was flat (80%, figure 4.3) in most of the participants with early-onset ANSD. In contrast, the rising configuration was more prominent in the late-onset ANSD group. It is reported in the literature that low-frequency cues are coded by the phase-locked responses of the auditory nerve fibres (Moore & Sek, 1996). Auditory nerve impairment affects the phase-locking abilities and can result in a predominantly low-frequency hearing loss (Zeng et al., 2005). Thus, it can be hypothesized that late-onset ANSD typically affects the auditory nerve leading to poor phase-locking abilities resulting in a rising type of audiogram configuration. This can also be attributed to the fact that low-frequency fibres have a longer course (Arnesen & Osen, 1978), making them more susceptible to neuronal pathologies than mid-frequency and high-frequency fibres, which are generally shorter. However, a flat audiogram configuration in participants with early-onset ANSD suggests a lesion more at the level of IHC or synapse leading to hearing loss at all frequencies (Dallos & Harris, 1978). These findings are in par with previous studies (Kumar & Jayaram, 2006; Narne et al., 2014). However, longitudinal studies are essential to substantiate the claim.

5.3 Effect of ANSD onset on Voice Characteristics

The results of MANOVA showed that the fundamental frequencies of all three vowels were increased in the early-onset group (figure 4.7). This finding is in par with previous studies of acoustic features in long-standing hearing loss cases (Campisi et al., 2006; Evans & Deliyski, 2007; Higgins et al., 1994; Horii, 1982). These results are attributed to poor laryngeal control (Giusti et al., 2001), greater laryngeal muscular tension (Ryalls & Larouche, 1992) or impaired internal auditory feedback (Nakamura et al., 2007). The fundamental frequency is the acoustic correlate of the pitch, which, when affected, impacts the social wellbeing of the individual (Campisi et al., 2006) and can be detected perceptually with voice quality rating scales.

The results of MANOVA also showed that the second and third harmonics (F_2 & F_3) of vowel /i/ of the late-onset ANSD group was significantly higher than the early-onset group (figure 4.7). This finding is suggestive of ANSD onset-based differences in the production of sounds with high-frequency harmonics. A comparison of the normative data

(Sreedevi, 2000) for format frequencies in Kannada speakers revealed that the late-onset sustained phonation characteristics (mean and SD) of the ANSD group for vowels /a/, /i/ and /u/ were similar to the adults in the same age range. However, the F_2 and F_3 in sustained phonation of /i/ for the early-onset ANSD group were relatively lower than the normative, indicative of lowering the pitch in the higher harmonics. The finding could be related to the group differences in the pathophysiology of the disorder, which gets manifested as a production deficit in voice. Pathophysiologically, patients with early-onset, are presented with a flat type of audiogram (equally impaired perception across all frequencies), whereas those with late-onset ANSD exhibit a rising type of hearing loss with less impaired high-frequency perception (Kumar & Jayaram, 2006). Thus, the impairment of high frequency sounds in the early-onset ANSD group, which occurs at a relatively younger age, places them at a disadvantage in perceiving F_2 & F_3 harmonics of /i/. The perception related disadvantage in this group can be postulated to transfer to the production-related aspect as well.

Furthermore, no significant differences in the formant frequencies of /a/ and /u/ can be attributed to the spectral component of these vowels. The formants of these vowels are much lower in frequency which is affected in both early and late-onset groups. Thus, the difference in formants was not seen in these vowels.

The production-related deficits originating from the perceptual disadvantage can be explained based on behaviourism learning theory (Watson, 1913), which advocates that learning vocal sound productions occurs by environmental conditioning, feedback reaction, and strengthening behaviour through repeated actions. According to this theory, the feedback received on the perception of the sound gets strengthened through repeated productions. The altered/distorted feedback in individuals with ANSD (Priya et al., 2018) right at childhood (early-onset) can lead to a deficit in the precise relay of vocal production to the auditory cortex. Thus, high-frequency sound productions through normal at the early stages get strengthened by the long-term vicious loop of feedback and altered perception in the early onset ANSD group, resulting in altered recalibration of high frequency perception. The perception of high frequency sounds in early hearing loss onset groups like those with even mild to moderate sensorineural hearing loss is documented in the literature (Smith et al., 2005). The relative lack of frequency shifts in late-onset ANSD (as opposed to early-onset group) is indicative of the very nature of delayed onset in this group, which otherwise would have affected their voice characteristics, especially the higher harmonic frequencies.

Although not significant, early-onset ANSD had more perturbations in pitch (jitter) and amplitude (shimmer), which also could be the result of poor phonatory control, as a result of poor feedback resulting in excessive air escape via the glottis (Bolfan-Stosic & Simunjak, 2007). Complimentary to this, the reduced harmonic-to-noise ratio in the early group is indicative of less periodicity (Teixeira & Fernandes, 2014) in voice in them (table 4.2, figure 4.10).

The group differences noticeable in the acoustic characteristics of voice were also noticed in the CAPE-V ratings by SLPs, indicative of perceptual voice manifestations of onset-related differences in voice quality between the two groups (figure 4.11). The overall voice ratings of the SLPs, were in strong agreement (figure 4.10) with each other, with only 6.43% of the errors recorded in overall voice quality ratings. Complimentary to the same, interclass correlation analysis also revealed high inter-judge reliability. This high degree of reliability in voice quality ratings between the five SLPs considered in the study ensures similarity and effective perceptual analyses of the voice samples.

The findings of MANOVA for perceptual parameters suggest that participants in the early-onset group have significantly higher roughness, breathiness and strain of voice than the late-onset group. This finding is in consensus with the literature reports of the voice of adults with early-onset hearing loss (i.e., the onset of hearing loss in childhood), who invariably demonstrated greater hoarseness, breathiness and monotonous voice compared to patients who showed symptoms of hearing loss at a later age (Coelho et al., 2015; Wirz et al., 1981). Breathy voice is most often the result of over aspiration in such cases to increase the tactile feedback, as the auditory feedback is compromised (Bolfan-Stosic & Simunjak, 2007). The reflections of disruptive neural firing right in childhood itself in early-onset ANSD can be postulated to limit their auditory feedback (Maruthy et al., 2019), which in turn manifests as difficulties in monitoring their speech. As a long-standing disruption in auditory neuronal firing, the early-onset group might have been at a serious disadvantage of poor auditory feedback for a long time. Similar findings of reduced vocal loudness in late-onset ANSD, with a long-standing duration (> five years) of the disorder, is reported in the literature (Maruthy et al., 2019). In contradiction to these findings, the present study revealed no significant difference in loudness across the groups. This could be because the earlier study compared long-standing ANSD patients with normal controls, whereas the present study included late-onset patients where loudness could be affected due to reduced self-confidence rather than any physiological basis. Thus, loudness-based voice differences (if any) between early and late-onset groups of ANSD might have been nullified as both the groups had poorer loudness owing, with the early-onset group with physiological basis and late-onset group with psychological basis.

5.4 Correlation between the variables

The presence of correlation between PTA, speech thresholds, degree and symmetry with fundamental and harmonic frequencies suggests that the possible differences seen in voice characteristics are a result of the difference in the audiological profiling between the groups (table 4.4). Further, the positive correlation between acoustic and perceptual analysis strengthens the use of perceptual severity rating scales when the facility for detailed acoustic voice evaluation, instrumentation, and infrastructure is unavailable, especially in developing countries like India. Thus, the voice evaluations can be done with an improved cost-benefit ratio. These results also strengthen the use of voice evaluations in cases where the audiological findings overlap due to the disorder's heterogeneity. Acoustic and perceptual voice evaluations can be used in such cases to confirm the onset reported by the patient.

5.5 Indicators of group segregation

The FLDA analyses revealed that PTA, speech thresholds and configuration were the best predictors of the group differences (table 4.5). This adds higher diagnostic value on the PTA and configuration, whose manifestations can be used as a valuable tool to verify the onset of the disorder, which are often retrospectively reported by the patient (especially in early-onset ANSD). While adults with late-onset have a lesser degree of hearing loss and a rising audiometric configuration, the early-onset ANSD group often demonstrate a greater degree of hearing loss and flat audiometric configuration. In addition, high fundamental frequencies and greater severity in the perceptual rating of voice are predominantly seen in the early-onset group compared to the late-onset group. The presence of such indicators should alert audiologists to reflect on the possible onset of the disorder, which in turn can facilitate their rehabilitation choice. While applications of cochlear implants in early-onset may be advisable (Fei et al., 2011; Kontorinis et al., 2014), the utility of hearing aids (Barman et al., 2016; Jijo & Yathiraj, 2021) or assistive listening in the late-onset group can be advocated as the first line of rehabilitation.

Chapter 6

SUMMARY AND CONCLUSIONS

Auditory Neuropathy Spectrum Disorder (ANSD) has been a research interest since its first description by Starr et al. (1996) due to its heterogeneous manifestations. Onset-based differences are underestimated in ANSD, especially when only auditory aspects are considered. Thus, the study aimed to describe onset-based differences using a new parameter, i.e. voice. The onset-based differences in audiological profiling and voice characteristics, the correlation between these two characteristics, and to predict those variables which best segregate the groups based on ANSD- onset is elucidated in the present study.

Thirty-one participants (14-31 years) were recruited for the study and were divided into two groups based on onset reported- early-onset group (onset reported to be before 12 years) and late-onset group (onset reported to be during or after adolescence). Audiological profiling was done retrospectively by studying the case reports (medical reports and demographic details). Audiological profiling consisted of pure tone audiometry, degree of hearing loss, the configuration of hearing loss, speech thresholds, the symmetry of hearing loss and the presence of cochlear microphonics. The participants were asked to record sustained phonations of three vowels (/a/, /i/ and /u/) on smartphones above specific configuration and send the voice sample over email to the experimenter. Acoustic parameters (fundamental frequency, harmonic frequencies, jitter, shimmer, harmonic-to-noise ratio) were assessed using Praat software. This was supplemented by perceptual evaluation (CAPE-V) by five speech-language pathologists.

Results revealed that the early-onset group had significantly higher PTA and speech thresholds, with more chances of being presented as symmetrical hearing loss. Also, most participants in the early-onset group had a flat configuration of hearing loss, in contrast to the late-onset group, which had a rising type of configuration. The voice analysis results revealed significantly increased fundamental frequency for all vowels and decreased F_2 and F_3 of /i/ in the early-onset group compared to the late-onset group, which can be explained based on differences in the pathophysiology of the disorder. This could also be attributed to the perception-production link; that is, as the perception of high frequency is affected in long-standing ANSD participants, the production of high-frequency sounds is also affected. Although not statistically significant, mean perturbations (jitter and shimmer) and harmonic-to-noise ratio were more affected in the early-onset group reflective of lowered auditory feedback and periodicity in their voice samples. These differences were also complemented by perceptual evaluation findings, which revealed greater severity of pitch, breathiness, strain, hoarseness and overall severity in the early-onset group.

It was also found out in the present study that the acoustic and perceptual parameters of voice was mild to moderately correlated with each other. Few audiological parameters had significant correlations with various vocal parameters. Thus, these results strengthen the use of voice evaluation when audiological characteristics are overlapping due to heterogeneity of the disorder. The FLDA analyses revealed that PTA, speech thresholds and configuration were the best predictors of the group differences. In addition, high fundamental frequencies and greater severity in the perceptual rating of voice are predominantly seen in the early-onset group compared to the late-onset group. The presence of such indicators should alert audiologists to reflect on the possible onset of the disorder, which in turn can facilitate their rehabilitation choice.

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