

# Chapter 8

## Auditory Neuropathy Spectrum Disorder

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Auditory Neuropathy Spectrum Disorder (ANSD) is a term recently recommended by an expert panel in the audiology profession to describe hearing loss characterized by normal or near normal cochlear hair cell function and absent or abnormal auditory nerve function.<sup>1</sup> Difficulty hearing in noise, fluctuating hearing, and speech perception performance not predicted by level of residual hearing have been reported (Starr et al., 1996; Rance et al., 1999). The incidence of ANSD in children with severe-profound hearing loss has been reported as 13.4% (Sanyebhaa et al., 2009).

(8<sup>th</sup> nerve). They advocate use of the term “neural hearing loss” to describe pathology in spiral ganglion cells or the central nervous system and “sensory hearing loss” to describe loss resulting from pathology in the hair cells.

In an effort to be consistent with recent terminology used in the audiology profession regarding this type of hearing loss, the term ANSD will be utilized in this chapter. The vast etiologies of ANSD result in a heterogeneous group of patients—each who must be managed methodically and individually for optimal communication and developmental progress. An understanding of what is known about ANSD and what remains unknown will assist the pediatric audiologist in appropriate identification and management of infants and children with this disorder.

Approximately 40% of ANSD cases have a genetic basis. Manchaiah and colleagues (2011) found the largest proportion of ANSD cases was due to syndromic, non-syndromic, or mitochondrial genetic factors. Inheritance patterns included autosomal dominant, autosomal recessive, X-linked, and mitochondrial.

Use of the term “neuropathy” to describe this disorder has resulted in much discussion in the audiology profession. Rapin and Gravel (2003) suggested “auditory neuropathy” is an inappropriate term to use to describe pathologies affecting the central auditory pathway and brainstem. They suggest this term is best suited to describe pathology limited to the spiral ganglion cells or their axons

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Various types of genetic mutations in ANSD result in different pathological changes in the auditory system.

Mutation to Connexin 26 (GJB2) genes accounts for 30-35% of autosomal recessive non-syndromic deafness. Cheng et al. (2005) studied over 700 children attending schools for the deaf or receiving services for moderate-profound hearing loss. Of those children, 76 tested had present OAE responses, suggesting a possible diagnosis of ANSD. No electrophysiological tests were conducted. Five of these children had GJB2 mutations. In a study by Santarelli et al. (2008), three children with GJB2 mutations had abnormal audiological and electrophysiological findings with preserved OHC functioning—confirming ANSD.

The OTOF gene (otoferlin) has been widely discussed in cases of ANSD. OTOF encodes for otoferlin, which is expressed in the cochlea and vestibule, in cochlear and vestibular nuclei, hippocampus, cerebellum, and testis. In adult cochleae, it is expressed only in inner hair cells at the basolateral region, where afferent synaptic contacts are located (Zadro et al., 2010).

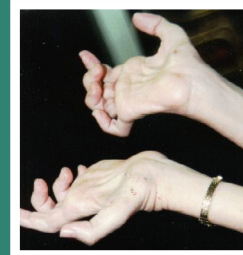
Pejvakin is a protein detected in the cell bodies of neurons of the afferent auditory pathway. It has been detected in some cases of autosomal recessive ANSD. DFNB59 encodes pejvakin and has shown to cause neural dysfunction along the auditory pathway in humans. Pejvakin is a paralog of DFNA5, which is also a protein involved in deafness (Delmaghani et al., 2006).

The MPZ gene (myelin protein zero) was the first gene associated with ANSD in patients with Charcot Marie Tooth Disease. MPZ encodes a protein included in the compact myelin that plays a crucial role in myelin formation and adhesion. A postmortem examination of one patient with this etiology of ANSD revealed preserved cochlear hair cells, decreased spiral ganglion cell number, and extensive degeneration of both peripheral and central processes in the residual axons. The proximal portion of the auditory nerve showed axonal loss and incomplete remyelination at the entrance to the brainstem (Santarelli, 2010).

Various types of genetic mutations in ANSD result in different pathological changes in the auditory system (Manchaiah et al., 2011). Continued clinical study of genetic etiologies of ANSD may hold information to assist in specific aspects of clinical management of cases. Syndromes ANSD has been associated with include:

- Charcot-Marie Tooth Disease (see *Figure 1*)
- Leber's Hereditary Optic Neuropathy
- Fredreich's Ataxia
- Mohr-Tranabjaerg Syndrome
- Refsum's Disease
- Mitochondrial disease

## Figure 1 Extremities of Patient with Charcot Marie Tooth Disease



Caused by mutations in genes producing proteins involved in the structure and function of peripheral nerve axon or the myelin sheath. Degeneration of motor nerves results in muscle weakness and atrophy in the extremities.<sup>4</sup> ANSD is reported to be associated with subtypes of this disease.

## Risk Factors

Risk factors which may contribute to ANSD include:

- Neonatal anoxia
- Neonatal hyperbilirubinemia
- Neonatal mechanical ventilation, hypoxia, or both
- Congenital brain abnormalities
- Low birthweight
- Extreme prematurity (< 28 weeks)
- Genetics or family history of ANSD

A higher risk of ANSD diagnosis is noted for Neonatal Intensive Care Unit (NICU) graduates (see *Figure 2*). The Joint Commission on Infant Hearing (JCIH, 2007) recommends auditory brainstem response (ABR) as part of the screening protocol for NICU babies admitted for greater than 5 days. NICU infants who do not pass the automated ABR screen should be referred directly to an audiologist for rescreen or comprehensive testing.

## *Figure 2* Low Birthweight and Extreme Prematurity Known Risk Factors for ANSD



### 1-3-6 Rule

The “1-3-6 rule” of screening for hearing loss by 1 month of age, confirmation of presence of hearing loss by 3 months of age, and intervention by 6 months of age is the goal of early detection and intervention of hearing impairment programs.<sup>3</sup> A diagnostic test battery of immittance, otoacoustic emissions, and threshold ABR testing will correctly diagnose cases of ANSD.

### Diagnostic Evaluation

Infants and children with suspected hearing loss should be referred to a

pediatric audiologist for comprehensive testing, which should include the following (see *Table 1*):

- Auditory Brainstem Response (ABR) Testing
- Case History
- Otoscopy
- Immittance
- Otoacoustic Emissions (OAEs)
- Behavioral Audiometry

### Case Management

Children with ANSD should be managed by a multidisciplinary team, which in addition to the pediatric audiologist includes a speech/language pathologist, teacher of the deaf and hard of hearing, otolaryngologist, geneticist, neurologist, pediatrician, and when necessary, physical and occupational therapists. Management must be considered on an individual basis—considering the unique abilities of each patient. Berlin recommends evaluating language growth and development every 3 months. If the patient does not make progress in language development, management and habilitation programs should be considered.<sup>1</sup>

A co-morbidity rate of 54% in ANSD patients has been reported in the form of developmental delays, learning delays, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, emotional and/or behavioral problems, uncorrected visual problems, blindness, cerebral palsy, motor disorders, apraxia, inner ear malformation, atretic or absent auditory nerve, seizures, and various syndromes.<sup>1</sup> These co-morbidities may contribute to speech/language and learning outcomes.

In patients with lack of speech/language progress, some benefit from amplification. Rance et al. (2002) compared unaided and aided speech perception assessments and cortical event-related potentials from 18 children diagnosed with ANSD and found that approximately half showed a significant improvement in open-set speech perception ability. Of these

# Table 1 Pediatric Audiologist Testing

## Auditory Brainstem Response (ABR) Testing

ABR testing using insert earphones click stimuli in alternating polarities at high-intensity levels (condensation and rarefaction, 80 or 90dBnHL) to look for the cochlear microphonic (CM; see *Figure 3*) is essential. Use of alternating clicks would yield a flat line if a genuine CM response existed (due to cancellation of the response). In patients with middle ear dysfunction and abnormal tympanometry, the CM response may not be recorded on ABR tracings.

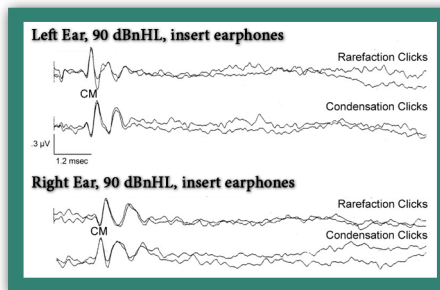
The insert earphone tubing can be clamped between the transducer and the ear tip to form an element of the test procedure, which validates the CM response or rejects a response as artifact. Care must be taken to position the tubing to form a loop or

curve to allow for it to be clamped (see *Figure 4*). Additional runs (either rarefaction or condensation polarity) should then be made at the same high-intensity stimulus levels. If the potential is clearly eliminated, a true CM exists (see *Figure 5*). If the measured potential remains, it is due to a stimulus artifact. The transducer and electrodes should be separated as much as possible, and retesting should be completed. It should be noted that the CM threshold is not a useful predictor of behavioral audiological thresholds.<sup>2</sup>

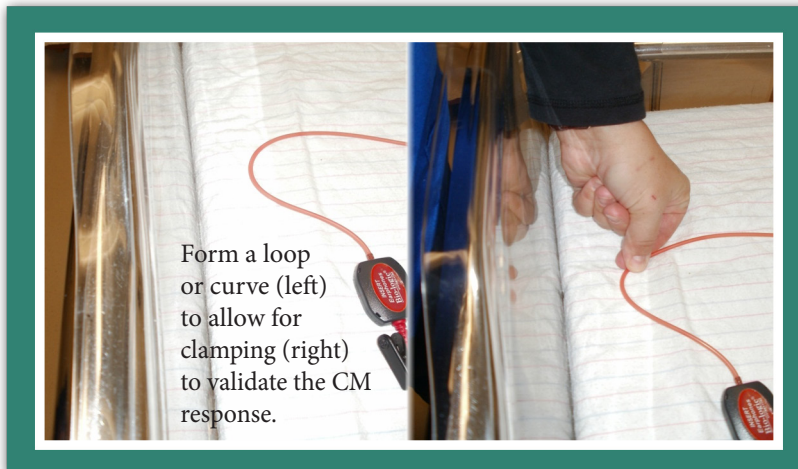
The largest and most identifiable CM responses in infants and young children with ANSD have been found between 0.5 and 0.8ms after stimulation. Maximal amplitudes of CM responses were found around 0.6ms after stimulus

delivery for patients with ANSD and normal hearing subjects. No significant differences were noted in patients with ANSD and absent DPOAEs when compared to patients with ANSD and present DPOAE responses in terms of CM time delay latency. CM amplitudes in patients with ANSD and absent DPOAEs were significantly lower than those in patients with ANSD and present DPOAEs—or a control group of normal hearing infants. The CM receptor potential originates from outer hair cells and inner hair cells. In cases of lower CM amplitudes in ANSD patients with absent DPOAEs, responses are likely from inner hair cells. Sites of lesion could be at the synapses between inner hair cells and the eighth nerve—or the eighth nerve (Shi et al., 2012).

*Figure 3*  
CM Response

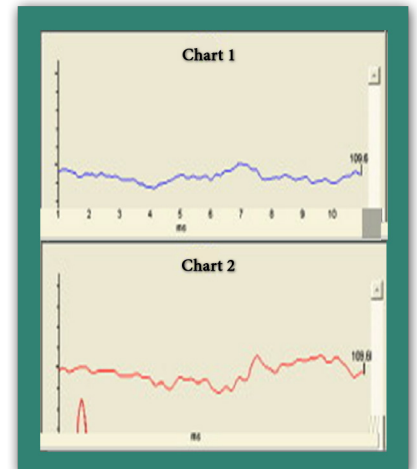


*Figure 4*  
Tubing Position



*Figure 5*  
ABR Tracing at High-Intensity Level with Tubing Clamped

Source: Mittal et al., 2012



# Table 1 (continued)

Case History	Otoscopy	Imittance
<p>Complete case history should be obtained from the family/caregivers and include prenatal and perinatal birth history, medical, developmental history, previous hearing screening results, known risk factors for hearing loss, and family/caregiver judgments regarding responsiveness to sounds.</p>	<p>Otoscopy should be completed to determine any obstruction or drainage in the external auditory canal and appearance of tympanic membrane.<sup>3</sup></p>	<p>A high-frequency probe tone should be utilized when testing infants below 6 months of age. The test reliability of the 1000Hz probe tone was found to be highly reproducible for healthy infants who had passed automated ABR and transient otoacoustic emissions (TOAEs) hearing screening (Mazian et al., 2010). Middle ear muscle reflex (MEMR) testing should also be completed in patients who are cooperative for testing. MEMRs have been found to be highly repeatable across test frequencies 0.5, 2, and 4kHz and for broadband noise in an ipsilateral stimulation mode (Kei, 2012). MEMRs are typically absent (possibly elevated) in patients with ANSD.</p>
Otoacoustic Emissions (OAEs)	Behavioral Audiometry	
<p>OAEs using a standard screening or diagnostic protocol to evaluate cochlear outer hair cell integrity should be completed. TOAEs or distortion product (DPOAE) stimuli are both appropriate. OAEs are typically present in patients with ANSD, although they may diminish over time (Starr et al., 2001).</p>	<p>Behavioral audiometry is recommended in addition to the above procedures using developmentally appropriate conditioned test procedures. Speech recognition in noise should be tested in older children, as this is often difficult for patients with ANSD and can provide useful information to assist in ongoing case management. Pure tone air and bone conduction thresholds are typically elevated in ANSD patients, and word recognition scores are very poor (Sininger &amp; Oba, 2001).</p>	



*Photo courtesy of Sound Beginnings/Utah State University*

ANSD is a complex hearing disorder requiring methodic identification and management techniques to achieve proper diagnosis and clinical outcomes.

children showing improvement, cortical-evoked potentials were present.

Some ANSD patients have used FM devices to enhance the signal-to-noise ratio of the listening environment and visual language support, such as cued speech. Some children with ANSD will benefit from cochlear implantation.<sup>1</sup>

Teagle et al. (2010) looked at over 140 patients with a diagnosis of ANSD. Over 40% were born prematurely, and 38% had abnormal preoperative magnetic resonance imaging findings of the brain and inner ear. Thirty-seven percent of these patients received cochlear implants, and 50% of those implanted demonstrated open-set speech perception abilities after

implantation. None of the patients with cochlear implants with cochlear nerve deficiency in the implanted ear achieved open-set speech perception abilities. Thus, a poor prognosis for development of open-set speech perception following cochlear implantation is predicted for this population.

ANSD is a complex hearing disorder requiring methodic identification and management techniques to achieve proper diagnosis and clinical outcomes. Each case should be approached individually by the multidisciplinary team. In addition to management according to speech/language progress, particular attention must be focused on anatomical findings from magnetic resonance imaging and comorbidities known for each patient.

## Reference Notes

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