Guidelines for

Identification and Management
of Infants and Young Children
with Auditory Neuropathy Spectrum Disorder

The Children's Hospital
® Bill Daniels Center for Children's Hearing

**Guidelines Development Conference
at NHS 2008, Como, Italy**

Guidelines for

Identification and Management of Infants and Young Children with Auditory Neuropathy Spectrum Disorder

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Preface

The "Guidelines Development Conference on the Identification and Management of Infants and Young Children with Auditory Neuropathy" evolved from an honorary Advances in Children's Hearing Lecture delivered by Yvonne Sininger, PhD, at the *Bill Daniels Center for Children's Hearing*, The Children's Hospital – Colorado, on the topic of "auditory neuropathy." As she updated that audience on the most current state-of-the-art in diagnosis and management of children with this disorder, Dr. Sininger also discussed the many questions and controversies about this perplexing and variable condition. After her thought-provoking lecture, Yvonne and I considered the possibility of developing an international conference with invited experts to share information and, hopefully, to arrive at some practical guidelines to help clinicians identify, diagnose, and manage infants and young children with this disorder.

As the idea of an international conference evolved, we concluded that a natural venue for such a conference would be the biennial NHS conference in Como Italy. Since 2000, Dr. Ferdinando Grandori and I have co-chaired the Newborn Hearing Systems (NHS) Conference to provide an international forum for scientists, clinicians, and parents to discuss issues relevant to the identification, diagnosis, and management of newborns and young infants with hearing loss. As this meeting grew over the years, it became apparent that an exceptional synergy emerged from the interactions of more than 500 participants from countries throughout Europe, Asia, Africa, Australia and New Zealand, and the Americas. After conferring with Dr. Grandori, Yvonne and I concluded that this venue was indeed the perfect place to host a guidelines development conference. We subsequently contacted a group of internationally recognized scientists and clinicians with expertise in the area of "auditory neuropathy" to invite their participation in this conference scheduled as a special component of the NHS 2008 Conference (19 – 21 June 2008). To our delight, each invited participant agreed to attend and to contribute not only an oral presentation but also a summary scientific paper in their area of expertise.

The panel of distinguished scientists and clinicians who assembled in Como Italy in June 2008 included Yvonne Sininger, PhD, Arnold Starr, MD, Christine Petit, MD, PhD, Gary Rance, PhD, Barbara Cone, PhD, Kai Uus, MD, PhD, Patricia Roush, AuD, Jon Shallop, PhD, and Charles Berlin, PhD. Given the expertise, experience, and stature of these individuals, it is not unexpected that the guidelines development conference exceeded our expectations for quality presentations, lively discussions, and active panel and audience participation. The guidelines and summary scientific papers contained in this volume reflect the joint contributions of these eminent professionals. (The titles of some of the contrbuted papers in this monograph have been changed to reflect the terminology recommended by the expert panel. Terminology in the body of these papers has not been changed and is printed as originally submitted.)

In future years, we will undoubtedly learn more about how to identify, diagnose, and manage individuals with "auditory neuropathy." In the interim, Dr. Sininger and I hope that clinicians will find these guidelines useful not only for identification and diagnosis of infants and young children with this disorder, but also for initiating a dialogue with parents and families about intervention options for their babies.

I am indebted to Yvonne Sininger for sharing her expertise and guidance in planning, developing, and implementing the conference. Neither the conference nor this publication would have been possible without her selfless contributions. Ferdinando Grandori offered unwavering support for inclusion of the untested concept of a "meeting within a meeting" at the NHS2008 conference. Through her organizational talents, careful attention-to-detail, and gracious kindness, Valerie Hernandez helped transform the concept of this conference from an exciting idea to a well-conducted reality. Jerry Northern added critical wisdom, editorial insight, and professional direction to the publication of this monograph. Lastly, the conference and publication were supported by substantial financial contributions by the Bill Daniels Center for Children's Hearing and the Kelley Family/Schlessman Family Scottish Rite Masons Chair in Childhood Language Disorders at The Children's Hospital – Colorado. To our fine panel, Yvonne Sininger, Ferdi Grandori, and my colleagues at The Children's Hospital, I am forever grateful.

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INTRODUCTION

"Auditory neuropathy" is a relatively recent clinical diagnosis used to describe individuals with auditory disorders due to dysfunction of the synapse of the inner hair cells and auditory nerve, and/or the auditory nerve itself. Unlike patients with sensory hearing loss who show clinical evidence of impaired outer hair cell function, patients with "auditory neuropathy" show clinical evidence of normally functioning outer hair cells. Individuals with "auditory neuropathy" typically demonstrate impaired speech understanding, and show normal to severely impaired speech detection and pure tone thresholds. It has been shown that "auditory neuropathy" affects an individual's ability to process rapidly changing acoustic signals, known as auditory temporal processing.

The range of functional hearing abilities in individuals with "auditory neuropathy" is vast. Some individuals experience little or no difficulty hearing and understanding despite abnormal auditory test results. Others complain of "hearing but not understanding, especially in background noise." Some individuals demonstrate fluctuant hearing abilities, reporting "good hearing days" and "bad hearing days." Finally, some children and adults with "auditory neuropathy" are functionally deaf. For infants and young children, the deleterious effect of "auditory neuropathy" on language development and academic achievement can be significant.

Audiological management and speech and language intervention for infants and young children with this disorder is challenging. Because the range of functional hearing ability in "auditory neuropathy" is so great, each child with this diagnosis is unique. Furthermore, because the developmental consequences of "auditory neuropathy" cannot be predicted on the basis of auditory test results obtained in infants, guidelines that exist for identification and management of infants and young children with "typical" sensorineural hearing loss (SNHL) do not entirely fit the special needs of infants with "auditory neuropathy."

To meet the need of the audiologists and other clinicians for guidance in identification and management of infants and young children with "auditory neuropathy," these guidelines were formulated by an expert panel of audiologists, hearing scientists, and physicians to reflect contemporary practice. This document is not intended to duplicate or replace current guidelines for identification and management of children with "typical" SNHL, but rather seeks to supplement these existing documents with recommendations specific to infants and young children

with "auditory neuropathy." As new information emerges, new techniques and strategies will undoubtedly evolve. In the interim, these guidelines for identification and management of children with "auditory neuropathy" offer practical guidance to audiologists and other clinicians, and families.

TERMINOLOGY

The term, auditory neuropathy, was originally proposed by Starr and colleagues (Starr et al., 1996) to describe the specific auditory disorder in a series of 10 patients, eight of whom demonstrated evidence of generalized peripheral neuropathy. The auditory disorder was characterized by evidence of normal cochlear outer hair cell function (preservation of otoacoustic emissions and cochlear microphonics) and abnormal auditory pathway function beginning with the VIII nerve (absent or severely abnormal auditory brainstem potentials).

Some investigators (Berlin et al., 2001a; 2001b; Rapin and Gravel, 2003; 2006) have expressed dissatisfaction with the term auditory neuropathy because the constellation of test results defining this disorder does not provide direct evidence of auditory nerve dysfunction or "neuropathy." Indeed, only a subset of individuals with this disorder will be found to have abnormal auditory nerve function. Other lesions, for example, mutation of the otoferlin (OTOF) gene, which results in synaptic dysfunction at the junction of the inner hair cell/auditory nerve, will produce the same constellation of auditory test results in affected individuals (Yasunaga et al., 1999; Yasunaga et al., 2000). To address this, and other concerns, Berlin and colleagues (2001a; 2001b) proposed the term "auditory dys-synchrony."

To address the potential confusion that arises from multiple designations for this disorder, the panel sought to identify simplified terminology that would unify the concept of an *auditory disorder* with a *range of presentations* secondary to a variety of etiologies. The panel considered multiple suggestions proposed by both panel and audience participants, and concurred that the most appropriate designation was "auditory neuropathy spectrum disorder" (ANSD). Three principle factors drove this consensus. First, despite potentially inexact usage, the term "auditory neuropathy" has gained wide-spread acceptance, both in the professional literature and among parent/consumer organizations. Renaming the disorder could lead to confusion for patients and professionals whereas retaining current terminology would provide continuity for the lay and scientific communities. Second, the expression of this disorder in everyday listening and communication behaviors encompasses a spectrum ranging

from limited or mild effects (complaints of difficulty "hearing" in noisy listening conditions) to profound effects (inability to "hear" in any listening condition, functionally "deaf"). Finally, the term "spectrum" was felt to expand the concept of this disorder to include sites of lesion other than the auditory nerve.

Starr and his colleagues (Starr et al., 2004) suggested segmenting the term auditory neuropathy into types, e.g. Type I (Pre-synaptic), Type II (Post-synaptic). In 2008, Starr and colleagues (Starr et al., 2008) proposed refining the terminology by site of disorder. For example, if the auditory nerve was involved but the inner hair cells and synapses were spared, the disorder would be classified as "auditory nerve disorder." Similarly, if the inner hair cell synapses were disordered but the auditory nerve was normal, then the term "auditory synaptic disorder" would be appropriate. Currently, there are no clinical measures to distinguish site of disorder with this degree of precision. The panel concurred that subtypes or site-specific classification would be helpful to define the disorder more specifically, and that future research efforts should be directed to develop such a classification system.

DIAGNOSTIC CRITERIA

ANSD is characterized by evidence of normal or near normal cochlear hair cells (sensory) function and absent or abnormal auditory nerve function. Therefore, the (minimum) test battery needed to diagnose ANSD requires tests of cochlear hair cell (sensory) function and auditory nerve function.

Minimum Test Battery Required to Diagnose Individuals with ANSD:

1. Tests of cochlear hair cell (sensory) function:

   a. Otoacoustic emissions (OAEs) for outer hair cell function: Standard screening or diagnostic protocol using Transient-Evoked OAEs (TEOAEs) or Distortion Product OAEs (DPOAEs), and/or

   b. Cochlear microphonics: Click-evoked auditory brainstem response (ABR) to high-level click stimuli (80-90 dB nHL), tested with positive and negative polarity clicks in separate trials, through insert earphones (Starr et al, 2001; Berlin et al, 1998). A trial run with the sound-delivery tube clamped should be used to differentiate between the CM and stimulus artifact (Rance et al., 1999).

2. Test of auditory nerve function:

   a. Auditory brainstem response (ABR) to high-level click stimuli (80-90 dB nHL). To avoid misinterpreting cochlear microphonics as components of the ABR, responses to positive and negative polarity clicks must be obtained in separate trials as described above. CMs

will show a characteristic reversal in polarity with reversal in polarity of the stimulating click; ABR will show a constant polarity regardless of polarity of the click (Berlin et al., 1998).

Additional Tests Useful for Diagnosing Individuals with ANSD:

Middle ear muscle reflexes (acoustic reflexes) are absent or elevated in individuals with ANSD (Berlin et al., 2005). Because normative data on acoustic reflex thresholds in very young infants using high probe-tone frequencies (1000 Hz) have not been established, this procedure is not required to diagnose ANSD. Nevertheless, a complete test battery for ANSD should include middle ear muscle reflex testing whenever possible.

Suppression of otoacoustic emissions by contralateral noise is abnormal in individuals with ANSD (Hood et al., 2003). Although this test has not gained widespread clinical usage, it is a potential candidate for further diagnostic studies in individuals with reliably recorded OAEs.

Special Considerations in Diagnosing Infants with ANSD:

Conventionally-recorded distortion product and transient OAEs are usually normal or near normal in individuals with ANSD. In newborns and very young infants, measurement of OAEs may be compromised by presence of residual fluid in the ear canal/middle ear (Doyle et al., 2000) or otitis media with effusion (OME). OAEs may be present initially and disappear over time in individuals with ANSD (Starr et al., 1996). Loss of OAEs, however, does not reflect change in auditory function or signal conversion of ANSD to typical SNHL.

Cochlear microphonics also provide a valid measure of hair cell function (see Cone in this volume for a discussion about the difference in generators of OAEs and CMs). CMs generally remain present in individuals with ANSD despite loss of OAEs (Starr et al., 1996). CMs are easily recorded from standard ABR recording protocols when insert earphones are used (Starr et al., 2001; Berlin et al., 2003). Stimulus artifact precludes effective recording of CMs when electromagnetic circumaural earphones are used (Stone et al. 1986; Berlin et al., 1998).

The auditory brainstem response (ABR) is markedly abnormal in individuals with ANSD. Recordings might appear as 1) a "flat" ABR with no evidence of any peaks or 2) presence of early peaks (waves up to III) with absence of later waves or 3) some poorly synchronized but evident later peaks (wave V) that appear only to stimuli at elevated stimulus levels.

When using these test procedures in newborns and very young infants, recording conditions must be optimum to obtain valid, artifact-free, unambiguous test results. Infants should be quietly sleeping in either

natural or sedated sleep to avoid movement artifact or "noisy" recordings. Caution should be used in interpretation of results when these tests are used in infants below 36 weeks gestational age. Repeated measures, over several weeks or months, are recommended to determine the reliability of test results. Because "transient" ANSD has been reported in a some infants (Madden et al., 2002; Psarommatis et al., 2006; Attias and Raveh, 2007), frequent monitoring by the ANSD test battery is recommended to establish the stability of test results, especially in the first two years of life.

Once the diagnosis of ANSD has been established, the infant should be referred for comprehensive medical, developmental, and communication assessments.

RECOMMENDED COMPREHENSIVE ASSESSMENTS

Many of the assessments recommended for infants with ANSD are similar to assessments recommended for infants with SNHL. (JCIH, 2007). The recommended assessments for infants with ANSD include:

1. Pediatric and developmental evaluation and history,

2. Otologic evaluation with imaging of the cochlea and auditory nerve (computed tomography, CT, and magnetic resonance imaging, MRI),

3. Medical genetics evaluation,

4. Ophthalmologic assessment,

5. Neurological evaluation to assess peripheral and cranial nerve function, and

6. Communication assessment.

Although not routinely recommended for infants and young children, vestibular assessment should be considered if developmental or otologic evaluation identifies potential vestibular disorder (e.g., nystagmus, delay in walking).

There are three principle reasons for infants with auditory disorders, including infants with ANSD, to receive comprehensive medical, developmental, and communication assessments. First, defining etiology of ANSD is important for predicting if the condition may be transient or is permanent (Madden et al., 2002; Psarommatis et al. 2006 Attias and Raveh, 2007), determining if medical or surgical treatment is needed, and answering parent's questions about cause of their infant's hearing disorder. Second, because infants with ANSD, especially those who received care in the NICU, are at-risk for additional disabilities, early identification of developmental delays is important for optimum child development. Third, infants with ANSD may develop additional cranial or peripheral neuropathies secondary to a specific diagnosis (Starr et al., 1996).

ANSD may be unilateral or bilateral. The possibility of cochlear nerve deficiency (absent or small cochlear nerves) should be considered for all children with ANSD, and especially for well-babies with unilateral ANSD and no medical history related to ANSD (Buchman et al., 2006) or infants with unilateral craniofacial anomalies (Carvalho et al., 1999). Contemporary imaging procedures (MRI and/or CT) are useful in these patients to assess integrity of the eighth nerve and internal auditory meatus.

Families of young infants benefit from early referral for communication assessment. Speech-language pathologists and deaf educators with expertise in early communication development can counsel families about the developmental sequence of pre-language, communicative behaviors, and support families in developing language-rich environments. Speech-language pathologists, deaf educators, and early intervention specialists can also help families monitor their infant's language development and assist families in evaluating the effectiveness of their chosen language development strategy.

RECOMMENDED AUDIOLOGICAL TEST BATTERY

The audiological test battery recommended for assessing functional hearing and monitoring auditory development in infants and toddlers with SHNL (JCIH, 2007) is appropriate for infants and toddlers with ANSD. This test battery consists of measures of middle ear function, behavioral response to pure-tones, and speech reception and speech recognition. These measures include:

1. Otoscopic examination and acoustic immittance measures of middle ear function. As with any infant, infants with ANSD may develop middle ear dysfunction and otitis media with effusion resulting in mild conductive hearing loss. Because middle ear muscle (acoustic) reflexes are absent or elevated in individuals with ANSD, otoscopy and tympanometry will be most useful for identifying infants with middle ear dysfunction.

2. Behavioral assessment of pure-tone thresholds using developmentally-appropriate, conditioned test procedures such as visual reinforcement audiometry (VRA), or conditioned orientation reflex (COR) audiometry. For very young or developmentally-delayed infants, behavioral observation audiometry (BOA) may be used to observe the infant's reflexive response to sound, however, results should not be interpreted as representing behavioral thresholds or minimal response levels.

3. Speech reception and speech recognition measures. For very young infants, response threshold to repetitive consonant-vowel combinations (e.g., ba-ba, ga-ga) is appropriate; for toddlers, pointing to body parts may yield acceptable speech threshold results. As children's vocabulary develops, speech recognition measures using standardized picture-pointing (e.g., Word Intelligibility by Picture Identification, WIPI {Ross and Lerman, 1970}; Early Speech Perception Test {Moog and Geers, 1990}) or open-set tests should be

employed. Standardized taped materials are preferable to live-voice presentation to obtain consistency of stimuli across test sessions and should be employed once children are old enough to repeat recorded materials. Because ANSD can significantly affect speech understanding in background noise, tests of speech recognition in noise or competing messages should be conducted as soon as developmentally appropriate.

5. Otoacoustic emissions utilizing either TEOAEs and/or DPOAEs. Although initially present, OAEs may disappear in individuals with ANSD (Starr et al., 2001; Deltenre et al., 1999).

Obligatory cortical auditory evoked potentials to speech or speech-like signals are not yet a standard clinical measure for infants or toddlers. These measures show promise, however, as objective clinical tools for predicting speech recognition performance in young children with ANSD (Rance et al., 2002; Cone-Wesson et al., 2003; Pearce et al., 2007).

Infants and young children with ANSD should receive frequent audiological evaluation to assess their behavioral response to sound and auditory development. Some youngsters with ANSD will experience fluctuations in detection thresholds for pure-tones (Starr et al., 1996; Rance et al., 1999; Rance et al., 2002). For children who demonstrate consistently elevated pure-tone thresholds, amplification should be considered to improve audibility of speech.

RECOMMENDED AMPLIFICATION STRATEGIES

For infants with typical SNHL, hearing aid fitting can proceed in the earliest months of life based on electrophysiological estimates (e.g., click ABR, ABR to tone bursts, and/or auditory steady state response) of hearing sensitivity. For infants with ANSD, however, electrophysiological methods do not predict auditory detection thresholds. Clinicians and parents must rely upon the infant's or young child's behavioral response to sound to guide the hearing aid fitting decision. If an infant or young child with ANSD demonstrates elevated pure-tone and speech detection thresholds with consistent test-retest reliability, hearing aid fitting should be considered and a trial use of hearing aids should be offered to families.

Hearing aid fitting strategies for children with ANSD should follow established guidelines for the fitting of amplification in infants and toddlers (The Pediatric Working Group of the Conference on Amplification for Children with Auditory Deficits, 2001; American Academy of Audiology Pediatric Amplification Protocol, 2003). Special considerations for infants and young children with ANSD include:

1. Infants and young children with ANSD should be fitted with amplification as soon as ear-specific elevated pure-tone and speech detection thresholds are demonstrated by conditioned test procedures (VRA or COR, see above). "Thresholds" or minimum response levels obtained by these techniques should be used to set amplification targets.

2. Significant improvement in auditory function, including "recovery" from ANSD, has been reported in some infants with this diagnosis ((Madden et al., 2002; Psarommatis et al., 2006; Attias and Raveh, 2007)). Careful monitoring of infant's auditory function by ABR and behavioral response by conditioned test procedures is required to adjust and modify amplification as needed. Although some risk factors for "transient" ANSD have been identified ((Madden et al., 2002; Psarommatis et al, 2006; Attias and Raveh, 2007)), at the present time, all infants and young children with ANSD, regardless of presumed etiology, should be carefully monitored for changes in auditory function and behavioral response to sound.

3. For infants with developmental delay where conditioned test procedures are unsuccessful, amplification fitting may proceed using behavioral observation of auditory behaviors and/or cortical evoked potentials when a) indications of auditory sensitivity are clearly outside developmental norms until more reliable measures can be obtained, and b) generally not before 6 months of age.

Temporal processing, or encoding the temporal characteristics of speech, is affected in individuals with ANSD (Zeng et al., 1999; Rance et al., 2004) resulting in a disproportionate loss in speech understanding ability relative to the individual's pure-tone thresholds (Starr et al., 1996; Rance et al., 1999; Rance et al., 2002). Although conventional hearing aids improve sound audibility, they do not resolve temporal processing deficits. Therefore, children with ANSD may not experience the same benefits from hearing aids expected from children with typical SNHL in whom temporal processing is relatively unaffected. Parental observation by formal questionnaire or survey (e.g., Infant-Toddler Meaningful Auditory Integration Scale, IT-MAIS {Zimmerman-Phillips et al., 2001}) may be helpful for assessing amplification benefit. In addition, speech recognition testing, including speech-in-noise or competing messages, should be incorporated into the hearing aid monitoring protocol as soon as developmentally appropriate for the child.

Strategies to improve the signal-to-noise ratio for children with ANSD should, theoretically, improve speech recognition and language learning (Hood et al., 2003). Trial use of an FM system, especially in structured and spontaneous language-learning activities, should also be considered for children with ANSD.

SPECIAL CONSIDERATIONS FOR COCHLEAR IMPLANTATION

Despite an adequate trial with appropriately-fitted amplification, some children with ANSD may demonstrate poor progress in speech

understanding ability and aural/auditory language development. For these children, cochlear implantation should be considered, regardless of behavioral audiometric thresholds.

In addition to standard cochlear implantation criteria for children, special considerations for cochlear implantation in children with ANSD include:

1. As noted above, significant improvement in auditory function, including "recovery" from ANSD has been reported in a subset of infants with this diagnosis. Families should be informed that spontaneous improvement in auditory function has been reported up to two years of age. Cochlear implantation, therefore, should not be considered until auditory test results (ABR and estimates of behavioral sensitivity) are stable and demonstrate unequivocal evidence of permanent ANSD (no change in or recovery of ABR). Deferring the decision for cochlear implantation until age two years may be appropriate. All infants with ANSD, including those being monitored for possible recovery, should be enrolled in early intervention and language stimulation programs to prevent delay in language acquisition.

2. Evidence of auditory nerve sufficiency should be obtained prior to surgery using appropriate imaging technology (Buchman et al., 2006).

3. Children with ANSD who do not demonstrate good progress in speech recognition ability and language development should be considered candidates for cochlear implantation *regardless of audiometric thresholds.* Children in this category with elevated pure-tone and speech detection thresholds should receive a trial of amplification fitted by pediatric amplification guidelines prior to consideration for implantation.

Emerging data suggest that pre-implantation electrical stimulation testing may be useful in determining CI candidacy in some cases (Gibson et al., 2007). At the present time, pre-implantation electrical stimulation is not a requirement for implantation.

Cochlear implants offer the possibility of improving auditory temporal processing by stimulating synchronous discharge of the auditory nerve. For example, ABR, which requires neural synchrony, can be electrically-evoked in many individuals with cochlear implants (Peterson et al., 2003; Shallop et al., 2003). Furthermore, speech recognition ability, which is strongly dependent on temporal processing ability, is similar in many cochlear-implant users with ANSD to speech recognition ability measured in cochlear implant users with typical SNHL (Madden et al., 2002, Mason et al., 2003; Rance and Barker, 2008). For families who wish to consider cochlear implantation for their child with ANSD, referral to a center with experience with managing children with this diagnosis is strongly encouraged.

RECOMMENDED HABILITATION FOR COMMUNICATION DEVELOPMENT

Families of infants with ANSD should be informed that their baby's auditory capacity or speech, language, and communication development cannot be predicted on the basis of the initial evaluation. Ongoing monitoring of their infant's auditory, speech, language, communication, and general development is essential. As with all infants and children with hearing loss (JCIH, 2007), families should be made aware of all communication options presented in an unbiased manner. Informed family choice and desired outcome guide the decision-making process. For most children with ANSD, use of any combination of communication systems that incorporates visual support is appropriate (e.g., auditory/aural with lipreading and natural gesture, cued speech, total communication, sign language). Decisions regarding mode of communication must ultimately be made by the family and respected by all professionals involved.

Infants with this diagnosis should receive referral to early intervention programs that assess the language, cognitive skills, auditory skills, speech, vocabulary, and social-emotional development of children at six month intervals during the first three years of life. Appropriate assessment tools include those that have been standardized on children with normal hearing and norm-referenced assessment tools that are appropriate to measure progress in verbal and visual language (JCIH, 2007).

SCREENING NEWBORNS FOR AUDITORY NEUROPATHY SPECTRUM DISORDER

The panel concurred with the Joint Committee on Infant Hearing 2007 Position Statement in which the definition of targeted hearing loss was expanded to include "neural hearing loss" in infants admitted to the NICU. Because screening by OAEs will fail to detect infants with "neural hearing loss" or ANSD, the panel further concurred with the JCIH recommendation that infants who receive care in the NICU for five days or more receive hearing screening by ABR.

Screening well-babies for ANSD is more problematic. In many well-baby nurseries, the hearing screening protocol is screening by OAEs. Although this technology will detect infants with sensory hearing loss, it will "pass" infants with ANSD. Even if the nursery uses a "two-stage" protocol, e.g., OAEs followed by automated ABR for those infants who "fail" OAE screening, infants with ANSD will not receive the second, automated ABR screening because they "passed" OAE screening. In those well-baby nurseries where automated ABR is the first screening technology, infants who fail this test should not be rescreened by OAEs and "passed" because these infants may have ANSD.

Because the probable cause of ANSD in well-babies is genetic, infants with a family history of childhood hearing loss or sensory motor neuropathy should receive hearing screening by ABR.

As more information becomes available on the prevalence of ANSD in the well-baby population, stronger recommendations for screening all infants for ANSD, regardless of nursery care level, may emerge.

For infants who "pass" newborn hearing screening, subsequent parent or caregiver concern about the child's auditory, speech, or language development should trigger a referral for audiological assessment including behavioral pure-tone and speech threshold measures, speech recognition testing (as developmentally appropriate), and tympanometry and middle ear muscle reflexes. Re-screening these infant's or young children's hearing with OAEs is not sufficient because such re-screening will "pass" infants and young children with ANSD.

MONITORING INFANTS WITH "TRANSIENT" ANSD

Some infants with an initial diagnosis of ANSD may demonstrate improved auditory function and even "recovery" on ABR testing (Madden et al., 2002; Psarommatis et al., 2006; Attias and Raveh, 2007). For those infants who "recover" from ANSD, the panel recommends regular surveillance of developmental milestones, auditory skills, parental concerns, and middle ear status consistent with the Joint Committee on Infant Hearing 2007 Position Statement (JCIH, 2007). Because the residual effects of transient ANSD are unknown, ongoing monitoring of the infant's auditory, speech, and language development as well as global (e.g., motor, cognitive, and social) development is critical. Those infants and young children whose speech and language development is not commensurate with their general development should be referred for speech and language evaluation and audiological assessment.

The Joint Committee on Infant Hearing recognizes sensory motor neuropathies such as Friedreich ataxia and Charcot-Marie-Tooth syndrome as risk indicators for delayed onset hearing loss (JCIH, 2007). Per the Joint Committee's recommendation, infants with a risk indicator should be referred for an audiological assessment at least once by 24 to 30 months of age. Given the possibility of late onset ANSD in infants with family history of sensory motor neuropathies, audiological assessment including ABR, OAEs, tympanometry and middle ear muscle reflexes is warranted.

COUNSELING FAMILIES OF INFANTS WITH ANSD

Counseling families of infants and young children with ANSD is one of the greatest challenges associated with this disorder. Because the developmental effects of ANSD cannot be predicted from test results obtained in the earliest months or even years of life, families struggle with the uncertainty of what the diagnosis means relative to their infant's growth and development. Many infants with ANSD have had difficult perinatal or neonatal courses with complications including prematurity, birth asphyxia, infections, or other conditions requiring neonatal intensive care. The significance of the ANSD diagnosis may be difficult for families to appreciate as they struggle to understand their infant's complex medical and developmental needs. Strong support systems, including parents of children with similar diagnoses and professionals with expertise in clinical social work and family counseling, should be available to meet the on-going and changing needs of families.

Clinicians working with infants and young children with ANSD and their families must remain flexible in approaching habilitative options. All members of the team, including the family, should be encouraged to question specific methodologies and strategies if the child's language and communication development is not commensurate with his or her developmental potential.

Children with ANSD can develop into healthy and dynamic citizens with happy personal lives, successful academic experiences, and satisfying careers. Clinicians should help families realize this goal by identifying and supporting the unique strengths and abilities of the child and family.

Participants in the "Guidelines Development Conference on the Identification and Management of Infants and Young Children with Auditory Neuropathy" included (from left): Kai Uus, Barbara Cone, Yvonne Sininger, Patricia Roush, Deborah Hayes, Charles Berlin, Ferdinando Grandori, and Jon Shallop. Not pictured: Gary Rance, Arnold Starr, and Christine Petit.

Yvonne Sininger, PhD

Auditory Neuropathy Spectrum Disorder: Challenges and Questions

It has been more than twenty years since I first saw the patient described as "Eve" (Sininger and Starr, 2001). Eve was our first introduction to a patient with an auditory disorder with symptoms that did not fit neatly into well-established notions about hearing loss. My training as an audiologist and as a hearing scientist had focused on the function and disorders of the cochlea - specifically of the organ of Corti. Audiologists or otolaryngologists generally assumed that if a person has a loss of hearing sensitivity, the disorder must reside in the middle ear or cochlea as the auditory nerve is considered just a conduit to the brainstem. My specialty was in using the auditory brainstem response (ABR) technology to predict hearing thresholds in infants and toddlers in whom a standard hearing evaluation was not possible. One thing I knew for certain was that the auditory threshold of the ABR was essentially the same as the threshold for detection of sound. Why then could patient Eve hear the click sound stimulus we presented to her ears, but show no auditory brainstem response tracings? My intuition was that something must be wrong with her auditory nerve but I had never encountered a similar case. We thought she was a single interesting case with unique clinical findings. Instead, she turned out to be the tip of an iceberg.

Ten years later, we held a conference to discuss this new clinical entity identified as "auditory neuropathy (AN)." During that conference we described numerous patients with AN, and discussed the possible sites of lesion with focus on the auditory nerve and inner hair cells (IHC); we evaluated the patients' response to auditory stimuli with a focus on disorders of timing; we described the known relationships to genetic disorders and we even discussed possible methods of rehabilitation including hearing aids and cochlear implants (Sininger and Starr, 2001). Although we had learned a great deal in that ten year period, many of the topics discussed at that early conference are still under discussion today.

What Shall The Disorder Be Named??

The term "auditory neuropathy" was coined by (Starr et al., 1996) to describe a group of ten patients collected from a variety of clinical sites who exhibited common symptoms including hearing loss, present otoacoustic emissions, absent or severely abnormal ABR, and poor speech perception. Starr noted that seven of the ten patients demonstrated signs of generalized peripheral neuropathy. The consensus was that a similar "neuropathy" could be attributed to the auditory nerve

in these patients to explain the hearing disorder. The term optic neuropathy had been used for a similar disorder of the optic nerve that produces a fluctuating vision disorder.

The term "sensorineural" had long been used to describe conditions with hearing disorders that were not conductive in nature. This term reflected a lack of specificity in diagnosis, particularly before hair-cell-specific (outer hair cell) techniques such as otoacoustic emissions were available to aid in determining the functionality of individual auditory structures. "Sensorineural" hearing losses were almost universally assumed to involve hair cell dysfunction with or without accompanying loss of auditory neurons. So with a clinical presentation of auditory sensory elements intact and in combination with a disordered auditory nerve emerged, the use of the term "sensorineural" to describe the condition was not acceptable.

Still, many were not pleased with the name auditory neuropathy. If the site of lesion is not the auditory nerve, they argued, the term "neuropathy" is inappropriate. Rapin & Gravel (2003) spoke out against the term "auditory neuropathy " based on the fact that the children who had suffered from neonatal hyperbilirubinemia, a common factor for found in children with AN, would certainly demonstrate lesions central to the auditory nerve in the cochlear nucleus. Shapiro and colleagues (Shaia et al., 2005), however, have clearly shown that jaundiced rats demonstrate abnormality of spiral ganglion cells and loss of large myelinated auditory nerve fibers. These findings are consistent with the loss of wave I and II in many children with auditory neuropathy" and a history of hyperbilirubinemia.

The presence of an otoacoustic emission does not rule out a specific disorder of the inner hair cell. Still, the outer hair cells (OHCs) are known to be more vulnerable than inner hair cells to insults such as noise (Liberman and Kiang, 1978) or ototoxicity (Huizing and de Groot, 1987) and it would be unusual for the inner hair cell to be damaged while the outer hair cells were spared. Harrison (1999, 2001) and others demonstrated that both carboplatin and hypoxia could induce an isolated inner hair cell (IHC) lesion in the chinchilla and that those animals displayed elevated ABR thresholds and enhanced otoacoustic emissions, mimicking the symptoms of human patients. These findings might suggest that the IHC was a plausible candidate for the site of lesion in AN except for the fact that platinum-

based chemotherapy agents will not spare the outer hair cells in species other than chinchilla (Taudy et al., 1992). Clinical study of platinum-based chemotherapy in children demonstrated that when ototoxicity occurred, otoacoustic emission amplitudes were diminished along with hearing thresholds (Knight et al., 2007). In fact, isolated disorder of the IHC in the human temporal bone is quite rare (Schuknecht, 1974). One study has described the condition in which outer hair cells are present and inner hair cells are missing (Amatuzzi et al., 2001) in the post-mortem of three premature infants. Their cochlea showed a reduction in the number of IHCs but normal complement of OHCs and neurons. Each had died before one month of age after a stormy peri-natal course. The audiologic history of the infants is sketchy, but it is not clear that the ABR would be abolished or even abnormal with more than 50% of inner hair cells surviving. Overall, evidence of a selective inner hair cell loss as the basis of auditory neuropathy is weak and could explain the symptoms of the disorder only in a very small subset of the population.

Recently, clear evidence has emerged that mutation of the otoferlin (OTOF) gene is found in a group of patients with profound deafness, evidence of a cochlear microphonic response and often with otoacoustic emissions. The OTOF gene is involved in synthesis of otoferlin protein which has been localized to the inner hair cell and functions in synaptic vesicle/cell membrane fusion (Yasunaga et al., 1999, Rodriguez-Ballesteros et al., 2003). Based on the symptoms produced including profound deafness, it seems clear that the mechanism of this type of auditory neuropathy is a blocking of the synapse at the inner hair cell-auditory nerve junction. Certainly, this disorder could not be considered a "neuropathy" in the traditional sense — further challenging choice of the name.

Berlin et al. (2001) proposed the renaming the disorder "auditory dys-synchrony," These researchers claimed that the term "neuropathy" would discourage the use of cochlear implants under the assumption that a diseased nerve would not respond to electrical stimulation. However, there is ample evidence that a healthy auditory nerve is not necessary for successful cochlear implant use. For example animal studies have shown that electrical stimulation can be an effective means to providing consistent stimulation and can produce an ABR in mice with a demyelinazation of the auditory nerve (Zhou et al., 1995). Most profoundly deaf patients with extensive inner hair cell loss have a concomitant diminished complement of surviving auditory neurons and yet perform reasonably well with cochlear implantation. Clearly, the condition of auditory neuropathy alone should not discourage cochlear implantation. Berlin also argues, correctly based on the Amatuzzi et al. (2001) study, that in some cases of AN there is no evidence that the auditory nerve is involved. It is not clear, however, how the term "dys-synchrony" is a better choice. Loss of inner hair cells would reduce or obliterate the overall neural

response but would not cause a dys-synchrony or timing disorder, which can be documented in the vast majority of these patients. The patients with an otoferlin-based disorder also would have a severely diminished neural response but not a dys-synchronous one. Dys-synchrony implies the involvement of the auditory nerve and does not describe all cases of what we now call AN, and is therefore as inefficient as "neuropathy" in describing the disorder.

Starr et al.,(2004) have suggested using the term auditory neuropathy "Type I" or post-synaptic when a patient has evidence of auditory nerve involvement and "Type II" or pre-synaptic when evidence of hair cell involvement exists. This would help to distinguish patients based on site of lesion but is not a complete solution for several reasons. First, the site of lesion may not be known or even easily inferred. The use of electro-cochleography is suggested to cast light on the site of lesion as discussed in the section on diagnostic criteria. Second, there is still the misnomer of "neuropathy" in a sensory cell or synaptic disorder.

Unilateral auditory neuropathy also presents a challenge to the name of the disorder. Recent information suggests that many cases of unilateral, congenital profound hearing loss with present otoacoustic emissions or cochlear microphonic, are due to an agenesis of the auditory nerve on one side (Buchman et al., 2006) rather than any type of neuropathy. Another case of unilateral cerebellopontine angle cyst in a newborn provided evidence of a rare, non-traditional etiology for a unilateral case (Boudewyns et al., 2008). Certainly these are not examples of "neuropathy," yet present audiologic findings that meet the criteria.

So the dilemma ensues. Is there a title for this disorder that encompasses all of the complexity of the constellation of symptoms that includes abnormal/absent ABR with evidence of hair cell function (cochlear microphonic and otoacoustic emissions)? Should the name reflect the symptoms or the etiology of the disorder? Does it matter if the name is inexact?

How Is The Disorder Diagnosed? In 2001, the diagnostic criteria for AN were: 1) elevated pure tone thresholds by air and bone conduction, 2) very poor speech discrimination, 3) absent middle-ear muscle (acoustic) reflexes, 4) absent ABR to any level of stimuli, 5) present cochlear microphonic and 6) present otoacoustic emissions (Sininger and Oba, 2001). Today the criteria are not as clear.

 A significant number of children with "the disorder" will lose their transient or distortion-product OAEs over time and the clinical significance or physiologic mechanism for this is unknown (Deltenre et al., 1999; Starr et al., 2000). At the same time, the cochlear microphonic appears to be unchanged in these same subjects. How is the loss of OAEs to be interpreted? There are many interpretations of the functional significance

of OAEs. Some would argue that the loss of the clinically measured, low-level OAE signifies the loss of the OHC motility or the cochlear amplifier. Liberman and colleagues (2004) have shown that at least the low-level generated distortion product otoacoustic emission (DPOAE) is absent in a strain of mutant mice lacking prestin which is responsible for the OHC motility (Zheng et al., 2000). Liberman's data supports the argument that the motility of the OHC is the primary source of the low-level OAE (as used in diagnosis of AN) in mammals.

Hearing thresholds do not seem to change in children when the OAE disappears. Was the cochlear amplifier not contributing to threshold sensitivity? This is difficult to explain. Why does the OAE disappear in up to 1/3 of children with "The disorder?" In some cases the OAE disappears even in children who have not used amplification. To add to the complexity, there is no concomitant change in the amplitude of the cochlear microphonic (CM) when the OAE disappears. The CM is a reflection of the depolarization/repolarization of both inner and outer, hair cells (Dallos and Cheatham, 1976), in response to deflection of the stereocillia. If the OHCs had lost their normal depolarization capacity, one would expect to see a large change in CM and conversely, no CM change would signify that the ionic exchange process in the hair cells has been maintained. Why then are the contractile properties non functional? Some would argue that loss of the OAEs would re-classify the loss as "sensorineural." It appears that the OHCs are present but not functioning at full capacity. Should we only consider patients with OAEs present as having AN? How do we classify a patient with absent OAEs and a robust CM? Or perhaps more to the point, what defines "normal sensory function"?

The degree of impairment of speech perception in subjects with "the disorder" is quite variable (Rance et al., 1999) as is the degree of hearing loss as measured by pure tone thresholds (Sininger and Oba, 2001). Does a patient with no ABR, present OAE and normal thresholds and very good speech perception scores have "the disorder?" How abnormal does the ABR need to be? Does the patient with a 25 dB hearing loss with ABR threshold to clicks at 50 dBn have "the disorder" or just a poorly measured ABR?

One of the most robust criteria for "the disorder" is the lack of acoustic or middle ear muscle reflex (Berlin et al., 2003). If a sensory loss is less severe than an average threshold of about 60 dB, the acoustic reflex should be present with a stimulus level of 85-110 dB. Acoustic reflex measurement is underutilized in many audiology clinics. One of the most powerful uses of this simple test is to rule out AN. Wende Hanks of Gallaudet University (personal communication) points out that presently no normative values exist for acoustic reflex threshold in infants using a 1000 Hz probe tone (recommended for tympanometric measures in infants). Because of the critical need for diagnostic criteria relevant to infants, the question of

adding the acoustic reflex as a critical element of the diagnostic criteria should be addressed.

Finally, in regard to clinical diagnostic assessments, several groups have suggested that trans-tympanic electro-cochleography (ECochG) may provide added information to help delineate site of lesion, specifically distinguishing between pre and post-synaptic lesions by careful assessment of the summating and compound action potentials (McMahon et al., 2008; Santarelli et al., 2008). To date, the evidence matching the patterns of ECochG results to human physiology is suggestive, but not conclusive, and wide scale use an invasive technique of this type may require further study and validation.

Implications for Newborn Hearing Screening. Neonates with "the disorder" will not be detected by a screening procedure that allows a "pass" based on an otoacoustic emission. However, many researcher/clinicians estimate that 10% of all infants with hearing disorders detected by appropriate neonatal screening show symptoms of "the disorder" (Uus and Bamford, 2006). The need to acknowledge the presence of this disorder and make adjustments in screening protocols is just now beginning to happen. The 2007 Joint Committee on Infant Hearing (JCIH) statement, in regards to the target disorder for newborn hearing screening, states that:

"The definition has been expanded from congenital permanent bilateral, unilateral sensory, or permanent conductive hearing loss to include neural hearing loss (eg, "auditory neuropathy/dys-synchrony") in infants admitted to the neonatal intensive care unit (NICU) Separate protocols are recommended for NICU and well-baby nurseries. NICU babies admitted for greater than 5 days are to have auditory brainstem response (ABR) included as part of their screening so that neural hearing loss will not be missed."

Changing the recommended screening protocol in the NICU will make a significant difference in age at which "the disorder" is identified in infants overall but does not address the early identification of such children who are graduates of the well-baby nursery. The decision was based on the assumption that "these disorders typically occur in children who require NICU care" but that statement is not documented well. Given the substantial portion of this population whose etiology is a recessive non-syndromic gene mutation, the need for screening protocols for systematic post-screening surveillance is warranted. Diagnostic audiologic test batteries for follow-up of failed screenings must be appropriately designed to acknowledge the possibility of present OAEs in combination with significant auditory dysfunction. However, given the realities of health care budgets around the world, protocol changes designed to identify "the disorder" will require hard data evidence of the numbers of infants affected.

Several studies have shown some spontaneous improvement in the abnormal auditory symptoms of infants over time. Madden et al. (2002) found improvement in audiologic thresholds in about half of an infant group within 15 months of identification. They mention that the most common etiologic factor in children in whom improvement was seen was hyperbilirubinemia. Another study specifically followed neonates with a preliminary diagnosis of AN and found a spontaneous recovery of the ABR in 13 of 20 infant who could be retested (Psarommatis et al., 2006). In this sample, low birthweight was the most reliable indicator of potential remission. These studies point out the importance of careful follow-up of all infants suspected of displaying "the disorder" and of appropriate family counseling regarding all possible outcomes including remission. Consensus should be obtained on the appropriate course of action for neonates who present with possible AN. Intervention should not be delayed but dramatic interventions, such as cochlear implantation, should only proceed when a clearly stable condition exists.

Genetic Evaluation. When the site of lesion cannot be examined, as is the case in sensorineural deafness, it can sometimes be inferred from information regarding genetic mutations in the patient. This is particularly important in non-syndromic disease. The advantage of having genetic information is clear from the studies of patients carrying the mutation of the Otoferlin (OTOF) gene. In this case, the genetic mutation on Chromosome 2p 22-23 is found to be responsible for the production of Otoferlin. The protein has been localized specifically to the inner hair cell and it's function in transmitter release has been determined (Yasunaga et al., 2000; Rodriguez-Ballesteros et al., 2003). Mutations in the OTOF gene may be responsible for a large percentage of non-syndromic "Auditory neuropathy" particularly in the Spain and related Spanish-speaking populations (Rodriguez-Ballesteros et al., 2008). This is information that gives evidence of the site and type of lesion in human patients that could not be obtained in any other manner. Such information would be invaluable to clinicians managing children with "the disorder."

A similar finding has revealed information regarding another type of deafness in which the gene encoding the protein pejvakin has been implicated in affected family members with symptoms of "The disorder" (Delmaghani et al., 2006). A missense mutation on chromosome 2q31.1-31.3 impairs a protein that is found in spiral ganglion cells of primary auditory afferent fibers and in the auditory brainstem pathways. Persons with this type of mutation show a pattern of neural hearing disorder. However, the complexities of the disorder have been emphasized recently when a mouse model was developed in which a mutation producing a premature stop codon onto the DFNB59 (pejvakin) gene was found to be manifested in the outer hair cell, producing a progressive sensory deafness (Schwander et al., 2007).

The other non-syndromic type of "the disorder" that has been described in detail is auditory neuropathy dominant-1 (AUNA1), a dominantly-inherited, progressive form of the disorder that maps to chromosome 13q14-21 (Starr et al., 2004; Kim et al., 2004). The gene has not yet been isolated for AUNA1 and consequently the exact mechanism for the loss of hearing is not known. However, affected family members demonstrate a progressive hearing disorder with ABR abnormalities, present otoacoustic emissions that may disappear over time, robust cochlear microphonics, poor temporal and speech processing but no evidence of other peripheral neuropathies on neurological examination. A better understanding of the nature and etiology of this disorder should emerge as more information is gained regarding the specific gene responsible.

If routine genetic testing were available for some of the known genetic mutations involved in neural types of hearing loss, many aspects of the clinical management would be made easier including differential diagnosis, prognosis and appropriate treatment. However, such testing is not routinely available and new mutations are being discovered all the time. It is clear that genetic information can be quite important in the management of persons with "the disorder" but it is not clear how or if that information will be obtained or used.

How Do We Effectively Rehabilitate "The Disorder"?
Discussions on appropriate rehabilitation strategies for persons with "the disorder" have been varied and controversial. Given that the symptoms of this disorder are sometimes distinct from those of sensory hearing loss, new approaches seem necessary. It is clear that the heterogeneity of this disorder demands that rehabilitation plans be individualized and carefully monitored for success.

How do we aid in the development of spoken communication for infants/children with "the disorder?" It is clear that the typical patient will have auditory system performance that will make development of speech perception skills and spoken language abilities in the linguistically naive listener (infants and toddlers) very difficult. For example, we know that the typical patient with "the disorder" demonstrates poor temporal resolution as measured by modulation transfer functions, gap-detection thresholds or temporal integration (Zeng et al., 1999; Rance et al., 2004; Rance, 2005, Zeng et al., 2005) and reduced speech perception capacity beyond what can be predicted by the loss of audibility and particularly poor speech perception in the presence of noise or competing messages (Rance et al., 2002; Zeng et al., 2005; Rance, 2005; Zeng and Liu, 2006b). Frequency or pitch resolution and localization ability, at least for low frequencies, is impaired in patients with "the disorder" but intensity-related perception is relatively spared (Rance et al., 2004; Zeng et al., 2005).

For reasons that are not entirely clear, threshold sensitivity as measured clinically with pure tones and plotted on the audiogram, is generally not normal in these patients and thresholds can vary from being within normal limits to indicative of a profound hearing loss or anywhere between (Sininger and Oba, 2001; Rance et al., 1999). In addition, some but not all patients with "the disorder" will demonstrate abnormal fluctuations in threshold sensitivity over time (Rance et al.,1999), sometimes changing very dramatically, from normal to severe, in minutes along with illness (Gorga et al., 1995; Starr et al., 1998).

A basic principle of auditory rehabilitation for children with hearing loss is to provide the child with "audible" consistent speech signal. This is generally accomplished by fitting appropriate amplification systems such as hearing aids and/or FM devices or cochlear implants. Some scientists and clinicians question the wisdom of using standard hearing aids with children with auditory neuropathy based on several arguments. One is that outer hair cells, as indicated by the presence of otoacoustic emissions would be vulnerable to noise trauma, another that the timing dysfunction could not be ameliorated by a simple amplification system and finally that amplification systems have not been useful in this population (Berlin et al., 2003). Certainly conventional hearing aids will not alleviate temporal processing disorder but could be expected to provide sufficient amplification to bring speech and environmental sounds into an audible range. In fact, studies of patients with "the disorder" using conventional amplification have shown that some portion (perhaps 50%?) of subjects will obtain functional benefit from the use of amplification (Rance et al., 2008; Cone -Wesson et al., 2001). Differences in the impressions and findings regarding use of hearing aids may be based on differences in fitting strategies and in the imprecision of testing protocols to measure the effectiveness of hearing aids in general.

It should be noted that preliminary processing strategies involving speech envelope enhancement have been studied and appear to provide some benefit in speech processing for patients with "the disorder". Such strategies have not yet been implemented in real time and are quite preliminary but may provide some hope for temporal processing dysfunction for the future. At the present time, personal frequency-modulated amplification systems (known as FM systems), either alone or in combination with hearing aids, have been suggested to be particularly important for use in children with "the disorder" because of the severe breakdown of speech perception in noisy background conditions.

The most appropriate approach to intervention and "mode" of communication is also controversial. Methodologies that emphasize "auditory/oral" communications such as auditory-verbal therapy are very popular for children with sensory hearing loss. These techniques emphasize the auditory mode while minimizing the dependence on visual information in the speech signal. However, many scientists/clinicians familiar with children with "the disorder" would argue for emphasis on visual information and the use of manual communication, speech reading or a visual system such as "cued-speech" along with spoken language because of the sometimes severe degradation of the encoded auditory speech signal (Berlin et al., 2003). Visual information or representation of speech can certainly help to fill in when auditory information is inadequate.

The following questions are unresolved regarding approaches to rehabilitation, especially for children with what we know as auditory neuropathy:

1. Should amplification systems (hearing aids or FM systems) be used to compensate for loss of sensitivity to sound?

2. If yes, how should these systems be fit? Monaural or binaural, low gain or fit-to-target for degree of hearing loss?

3. Should compression amplification, known to add to temporal distortion of the amplified signal, be avoided? If so, how is noise trauma avoided with loud sounds?

4. Should children with OAEs using personal amplification devices be monitored for OAE reductions? If the OAE disappears, how can the cause be validly determined, given that OAEs may disappear without amplification? Should amplification be avoided in children with otoacoustic emissions? If so, how is loss of audibility compensated in children with present otoacoustic emissions?

5. How can auditory threshold fluctuations be managed with amplification devices?

6. What criteria should be used to determine if a cochlear implant evaluation should be initiated?

When and why is a cochlear implant appropriate for these patients? Clinical experience has shown that most patients with "the disorder" who undergo cochlear implantation show dramatic improvement in speech perception ability (Trautwein et al., 2001; Shallop et al., 2001; Peterson et al., 2003). However, although improvement in speech perception is found in the majority of patients, some studies have found that overall, the performance of patients with "the disorder" who are implanted is slightly poorer than seen in implanted patients with sensory type deafness (Zeng and Liu, 2006a) and an occasional implant patient may not receive any benefit (Rance and Barker, 2008).

Given these somewhat optimistic results and questionable performance of patients with hearing aids, many clinicians feel that implantation should be expedited in these patients, even when hearing sensitivity is better than that of patients who are generally considered eligible for implantation. If aided speech perception is poor, even when sensitivity is only moderately impaired, the current clinical standard for patients with "The disorder" is cochlear implantation.

The following are important questions regarding cochlear implantation of these patients. Given the uncertainty regarding the site of lesion in most patients with "the disorder" can clinicians insure that cochlear implantation will be effective? Should the United States Food and Drug Administration's (FDA) cochlear implant guidelines regarding the necessary degree of hearing loss be relaxed in these patients or can the speech perception deficit criteria be sufficient to justify implantation of these patients? Can the presence/absence of the auditory nerve be determined adequately and should this be tested in all patients? Does the fact that some patients symptoms are relieved over time indicate that we should wait to implant children with AN? What age is appropriate to implant these children with a cochlear implant?

Summary. The disorder (i.e, known generally as auditory neuropathy) has taught us a great deal about the normal and abnormal functioning of the human auditory system. Many questions still remain regarding the physiological nature of the disorder and how to determine it in individual patients, how it should be detected and diagnosed and how the disorder should be monitored and managed. All these questions cannot be answered at this time. Our challenge is to determine the current state of knowledge as a baseline, and then suggest future directions for research and investigations and to provide guidance for clinicians working with these patients.

Arnold Starr, MD

Auditory Neurosciences and the Recognition of Auditory Neuropathy

The auditory system's ability to encode temporal features of acoustic signals is essential for speech comprehension, localization of sound sources, and distinguishing auditory signals of interest from competing background noises. "Auditory neuropathy" is a clinical diagnosis used to describe patients with auditory temporal processing disorders who "can hear but not understand speech". This clinical problem is due to disordered auditory nerve activity due to abnormalities of auditory nerve, inner hair cells, and/or their synapses (Starr et al., 2008). In this paper, I will review the early auditory neuroscience studies that led to the identification of this special type of hearing impairment, along with some of the features of the disorder, and suggestions for future diagnostic, research and management directions.

Almost 80 years ago electrophysiology had advanced to allow analysis of fundamental properties of sensory systems. There were several key studies in experimental animals that identified electrical potentials generated by cochlear sensory cells and auditory nerve. The experiments of Wever and Bray in 1930 (http://www.nap.edu/html/biomems/ewever.html) in which an electrode had been placed on the auditory nerve of the cat and revealed alternating current (AC) potentials to tones that closely resembled the pressure waves of the acoustic stimuli. Their demonstration that a loud speaker in another room could transduce the potentials recorded from the nerve evoked by a tone or a speaker was more than exciting. Wever and Bray identified the source of the potentials as originating from the nerve since they disappeared when the nerve was transected distal to the placement of the electrode. Wever and Bray did not examine the cochlea after their nerve transactions and missed that the procedure also severed the blood vessels in the nerve interrupting the blood flow to the cochlea. Adrian et al. (1931) one of the eminent physiologist of that period, showed that the potentials were actually generated by the cochlea itself and reflected mechanical motions of sensory hair cells. The term "microphonics" was applied by Adrian et al. as the potentials were quite similar in appearance to those generated by mechanical taps on microphones. Hallpike and Rawdon-Smith (1934) did detailed experiments showing that both cochlear and neural elements contributed to these "mircophonic" potentials, www.pubmedcentral.nih.gov/articlerender. fcgi? artid=1394324. Davis and Saul showed that the auditory nerve potentials were of lower amplitude than the microphonics but both nerve and cochlear potentials faithfully reproduced the low frequencies of human speech sounds. The nerve potentials became known as neurophonics and the cochlear potentials as microphonics. Thus, cochlear microphonics and neurophonics are examples of the coordination of receptor and neural elements in encoding temporal features of the acoustic stimulus..

A critical step for the definition of objective measures of auditory nerve and cochlear activities was the development of computer based averaging of brain activity time locked to the stimulus developed by Clark et al. (1961) at the MIT computer Laboratories outside of Boston. The computer was capable of storing and summing individual time locked events and presenting an averaged potential to repetitions of the same stimulus. I had the opportunity in 1962 to use one of the first computers for the laboratory that came to be known as the LINC. I was studying auditory pathway activities in behaving cats implanted with electrodes in both cochlea, brainstem, thalamic, and cortical auditory sites. I could view the potentials from each of the electrodes along the pathway in response to sounds and then analyze them for time of arrival and amplitude. It was time consuming. We connected the output of cochlea electrode to the LINC and within a short time defined averaged potentials that had many deflections lasting over five ms. I appreciated the complexity, but not the significance, of the findings that would eventually lead to the far field recording activity of the auditory nerve and brainstem pathways by scalp electrodes. These potentials came to be known by many names including the auditory brainstem response (ABR). Averaged auditory potentials were soon demonstrated for auditory cortex by Geisler at MIT and Hallowell Davis (1976) in St Louis, and then for auditory nerve and brainstem by Jewett and Williston (1971) at UCSF and Sohmer and Feinmesser (1967) in Israel. These averaged potentials provided a window on activities of populations of neurons at several levels of the auditory pathways leading in the 1970's to identifying thresholds of "hearing" in children and infants by Galambos and Hecox (1978). At my laboratory in University California at Irvine, we used the ABR technique to identify site (s) of auditory neural dysfunction. ABR is now used routinely as a screening test for "hearing" (or is it "deafness"?) or to determine the functionality of auditory nerve and brainstem pathways in newborns.

One of the first descriptions of abnormal auditory temporal processes affecting both perception and ABR results was reported by Hausler and Levine (1980) in patients with known brainstem lesions affecting auditory pathway. These patients had elevated thresholds for interaural time differences for lateralizing binaural signals whereas interaural intensity cues were processed normally. The ABRs in these patients showed abnormalities of binaural integration of inputs from the two ears whereas monaural perceptions and ABRs were normal.

The ABR as an Objective Measure of Auditory Temporal Processes.

An 11- year-old patient was referred to me who demonstrated absent ABRs and only mild hearing loss. When I first saw Eve in 1989 (along with David McPherson), we confirmed that ABRs were absent but cochlear microphonics were indeed present. Otoacoustic emissions, which became available the following year, were also present. Eve described her problem as being able to "hear but not understand." Her neurological examination was entirely normal. Her speech understanding was very impaired, beyond that normally seen in persons with mild hearing threshold elevation. ABRs, middle latency and cortical response components were all absent. Her visual and somatosensory evoked potentials were present. Psychophysical measures with the help of Fan Gang Zeng and Bob Shannon showed abnormal use of temporal cues (thresholds for detecting brief silent gaps, lateralization of binaural stimuli using time cues, binaural beats, masking level differences, discrimination of low frequency pitch change). In contrast, discrimination of changes of intensity or of high frequency pitch changes were normal. The story of "Eve" was published in 1991 with nine authors (Starr et al., 1991) as an example of impaired auditory temporal processes affecting both auditory percepts and auditory evoked potentials likely due to a disorder of auditory nerve, inner hair cells, or their synapses in the presence of preserved outer hair cell functions. Other patients with absent ABRs and preserved OAEs were soon being identified. (Kraus et al., 1984; Berlin et al., 1993; Kaga et al., 1996). In retrospect, Hallowell Davis had identified these same ABR exceptions to the rules in approximately 2-3% of children when he first used ABRs in the early 70's.

Yvonne Sininger and I soon saw more adults and children with the same clinical picture. We discussed our patients with Terry Picton and Chuck Berlin at Louisiana State University (LSU) Medical Center, and learned that they also had patients with the same constellation of findings. We all met in New Orleans to see these patients to re-examine these patients as a group. When I examined the patients neurologically, eight of them had clear clinical evidence of a generalized peripheral neuropathy. Even Eve, who had normal findings in 1989, now had clinical evidence of the neuropathy. We opted that the disorder be called "auditory neuropathy" and it was also understood that the auditory nerve, and or its synapse with inner hair cells, could also be sites in the auditory periphery that when affected would lead to a relatively specific auditory temporal processing disorder (Starr et al., 1996).

Our group at LSU proposed three objective clinical measures for adults and children that would lead to the diagnosis of auditory neuropathy. These tests included:

1. Absence or severe abnormality of the ABR (in adults and children that would be beyond that seen for the degree of threshold elevation; (at this time the use of ABRs as a newborn hearing screen was just in its infancy).

2. Presence of the cochlear microphonics (CM) and/or otoacoustic emission (OAE). This clarification was needed since approximately 1/3 of the "auditory neuropathy" patients lose the OAEs but still have CMs.

3. Absence (or marked elevation) of acoustic middle ear reflexes

In addition to these diagnostic markers, we felt that there were important additional criteria that require behavioral testing:

4. Speech perception (reception) that is impaired beyond what would be expected for the degree of hearing threshold elevation. The use of this criterion is, of course, not appropriate for newborns and infants or for those with a profound hearing loss which would prevent speech reception and other psychophysical studies.

5. Ancillary criterion included a trial of personal amplification which is not of benefit for improved speech comprehension.

Auditory Neuropathy: The Disorder. We now know that auditory neuropathy (AN) has multiple etiologies and affects all age groups. Although the clinical expression of the disorder appears to be similar across the range of etiologies and sites of affliction in the auditory periphery, the degree of the symptoms may vary widely. The course of the disorder varies from being stationary, progressive or even to improving (Attias et al., 2007). Auditory neuropathy can be asymptomatic and that fact should not be startling as many medical disorders are detected by laboratory tests before symptoms are experienced. The spectrum of etiologies seems to change with age. Newborns with AN typically have metabolic abnormalities as many are critically ill with hypoxia, hyperbilirubinema, and infections. Healthy newborns with AN identified by universal neonatal auditory screening using ABR and OAE testing are typically due to genetic factors. When children enter school and receive mandatory hearing screening, no doubt additional individuals with hearing impairment will be identified, and some of those children will likely have additional objective tests consistent with AN. The etiologies in this school-aged group are still incompletely recognized but include genetic, immunological, infectious, neoplastic, congenital, and metabolic causes (Sinninger and Starr, 2001).

Cochlear implants appear to work well in some AN patients. The CI is now the treatment of choice for many children with bilateral profound sensorineural hearing loss. However, some AN subjects do quite well with amplification or cochlear implants and some do well even without treatment. It is an important caveat to remember to treat the patient and their symptoms, and not the lab test used for diagnosis.

Summary. The future challenge for us is to define the underlying molecular mechanisms of these "auditory neuropathy" disorders and their measure and document their effects on inner hair cells, synapses with auditory nerve terminals, and the function of auditory nerves. This new knowledge will allow the development of focused therapies for specific etiologies of auditory temporal processing disorder known as "auditory neuropathy."

GARY RANCE, PHD

Auditory Capacity in Children with Auditory Neuropathy Spectrum Disorder

Identification of children with auditory neuropathy through the comparison of pre-neural (otoacoustic emission/cochlear microphonic) and neural (auditory brainstem) responses is now relatively straightforward. However, determining auditory capacity in affected youngsters and using this information to devise appropriate intervention strategies remains a significant challenge.

Speech Perception

Impaired speech understanding is a consistently reported consequence of auditory neuropathy (AN) type hearing loss. Most affected adults have shown perceptual deficits greater than would be expected from their audiometric (sound detection) levels (Rance et al., 2008; Starr et al., 1996; Starr et al., 2000; Zeng et al., 2001). Findings in children have been more varied with some individuals performing at levels similar to their peers with sensorineural hearing loss, while others show little or no capacity to

understand speech despite (in many instances) enjoying complete access to the normal speech spectrum. This broad spread of perceptual abilities is reflected in Figure 1 which shows open-set speech perception score plotted against average hearing level for all of the children described in the literature thus far.

Understanding speech in the presence of background noise appears to be a particular problem for both adults and children with AN (Kraus et al., 2000; Rance et al., 2008; Starr et al., 1998). The mechanism underlying this excessive noise effect is not yet understood, but similar findings have been reported for less complex stimuli. Psychophysical studies have indicated that AN listeners
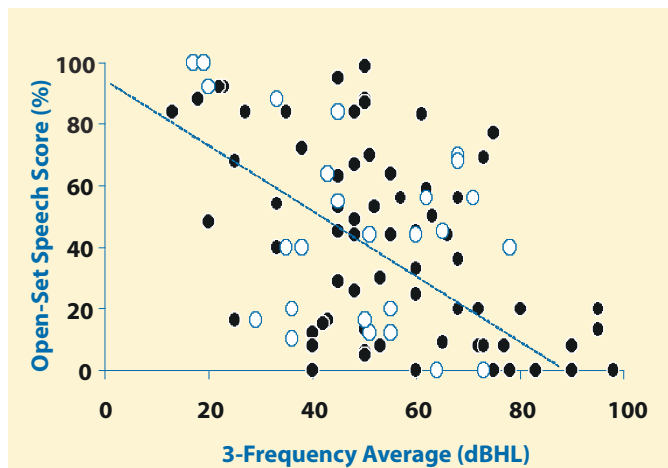

Figure 2. *CNC phoneme scores at four different signal-to-noise ratios (+20, +10, +5 & 0 dB). The filled circles represent the findings for 25 normally hearing children aged between 6 years and 12 years at assessment (Rance et al. 2007). The open data points describe the results for a 7 year old subject with AN/AD type hearing loss.*

Figure 1. *Open-set speech perception score / average hearing level comparisons for 108 children with AN/AD type hearing loss. The filled data points represent findings from open-set word tests and the open points show open-set sentence test results. The dashed line represents the minimum expected score for ears with sensorineural hearing loss (Yellin et al., 1989). Data for this meta-analysis were obtained from the following studies: Berlin et al., 1996; Konradsson, 1996; Kumar and Jayaram, 2005; Lee et al., 2001; Michalewski et al., 2005; Miyamoto et al., 1999; Narne and Vanaja, 2008; Picton et al., 1998; Rance et al., 2004; Rance et al., 2007; Sininger et al., 1995; Starr et al., 1991; Starr et al., 1998; Zeng et al., 2005; Zeng and Liu, 2006.*

are more effected by both simultaneous masking (where the signal is presented within the noise) and non-simultaneous masking (where the signal occurs immediately before or after the noise) than normally hearing subjects (Kraus et al., 2000; Vinay and Moore, 2007; Zeng et al., 2005).

The degree to which a competing signal can disrupt speech perception in children with AN/AD is demonstrated in Figure 2. The open data points

represent CNC-phoneme scores at four signal-to-noise ratios for a 7 year old with Friedreich Ataxia, the AN result pattern, but a normal audiogram. The filled data points show the findings for a group of healthy, normally hearing children of similar age (Rance et al., 2007). Listening in quiet (+20 dB SNR) was clearly not an issue for this AN/AD child, but even in relatively low levels of background noise he showed negligible speech perception ability. As signal-to-noise ratios in the average classroom are typically only 0-3 dB (Crandell and Smaldino, 2000) it is not surprising that both he and his teachers had reported significant problems at school.[1]

Disruption of Auditory Cues

The mismatch between speech understanding and the behavioural audiogram in individuals with AN/AD suggests that signal distortion rather than audibility is the factor limiting perception. A number of psychophysical studies carried out over the last decade have investigated the ways in which this distortion may affect auditory processing, and have identified a pattern of perceptual disruption that is quite distinct from that seen with other forms of permanent hearing loss. For example, as the cochlea is responsible for the initial processing of spectral cues, sensorineural hearing loss typically results in a loss of "frequency resolution" - the ability to perceive different components in a complex sound (Moore, 1995). As cochlear (outer hair cell) function in ears with AN/AD appears normal, it is not surprising to find that frequency resolution has been unimpaired in most reported cases (Caccace et al., 1983; Rance et al., 2004; Vinay and Moore, 2007).

In contrast, AN/AD by disrupting the timing of neural signals in the central pathways, affects aspects of auditory perception based on temporal cues.[2] This results in a range of deficits in both monaural and binaural processing, the degree of which is strongly correlated with the ability to understand speech (Rance et al., 2004; Zeng et al., 2005). In particular, the ability to perceive rapid changes in auditory signals over time (temporal resolution) can be severely compromised. This has been reflected both in "gap detection" tasks, where AN/AD listeners typically require a silent period of ≥20 ms (compared to <5 ms in normal subjects) before they become aware of a change in a continuous signal (Starr et al., 1991; Zeng et al., 2005) and "amplitude modulation detection" experiments where individuals with AN/AD show an impaired ability to track fast, and even relatively slow (<10 Hz) amplitude envelope changes over time (Rance et al., 2004; Zeng et al., 2005).

Impaired binaural processing, reflecting a reduced ability to integrate

subtle interaural timing cues has also been demonstrated in AN/AD listeners. Masking level difference (MLD) results for example, which reveal the release of masking obtained when inputs to the two ears are presented out of phase, are consistently abnormal in affected subjects (Starr et al., 1991; 1996) as is the ability to use interaural timing differences to judge sound direction (Zeng et al., 2005).

Temporal Processing and Speech Perception

In order to understand running speech, or even discriminate sounds within individual words, a listener must be able to perceive the characteristic shape of individual phonemes, and be able to follow the rapid within-phoneme changes that give cues to co-articulation. It is this need to cope with the dynamic nature of speech that poses the greatest challenge for individuals with temporal processing problems.

The specific effects of AN on speech perception are yet to be fully investigated but some particular problems (at the feature level) have been identified. Kraus et al., (2000) have shown that an inability to detect gaps in the speech signal can affect the perception of brief vowel features such as 3rd formant onset frequency. Furthermore, Narne and Vanaja (2008)
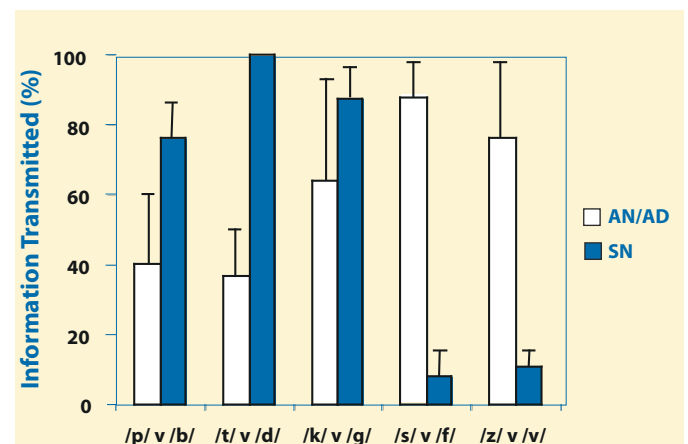
Figure 3. *Information transmitted for three stop-consonant pairs (/p v b/ /t v d/ k v g/) and two fricative pairs (/s v f/ /z v v/). Error bars represent one standard deviation.*

have suggested that perception of consonant place of articulation is disrupted in AN/AD listeners as a result of their inability to track rapid spectro-temporal changes in the signal (particularly for stop consonants).

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1 This child has subsequently been trialled with a radio-frequency listening device (to improve his classroom signal-to-noise ratio) and has shown dramatic improvement.
2 Temporal processing in ears with sensorineural hearing loss tends to be relatively unimpaired (Rance et al., 2004).

Recent work from our own laboratory (Rance et al., 2008) has examined the speech perception consequences of temporal processing disruption in a group of Friedreich ataxia patients with AN. In this study we carried out "information transmission analyses" to determine the pattern of perceptual errors on open-set word testing in three subjects (6 ears) with AN and 3 matched individuals with SN hearing loss. In particular we examined the confusions made between three phoneme pairs that were similar in each of their articulatory features apart from voicing /p & b/, /t & d/ and /k & g/. As such, the most salient difference in each phoneme pair was the voice onset time (the period required for vocal cord vibration to resume after the consonant). As can be seen in Figure 3, the AN listeners struggled to hear the difference in this silent period (which in the case of /p & b/ for example, is approximately 10-30 ms) while their SN counterparts had little difficulty. In contrast, perception of consonant place of articulation in the pairs /s & f/ and /z & v/ which is based on discrimination of high frequency spectral cues, was relatively unimpaired in the AN listeners but poor in those subjects with SN hearing loss.

In addition to the perceptual problems associated with brief speech stimuli, further investigation may reveal more generalized temporal-processing related consequences for individuals with AN. Impaired temporal resolution for example, may impact upon a listener's ability to use the cues contained within the overall speech amplitude envelope (Shannon et al., 1995; Turner et al. 1995). Furthermore, a reduced ability to separate sounds occurring successively (as suggested by forward and backward masking studies [Zeng et al., 2005]) may also result in excessive intra-speech masking effects, where loud (vowel) sounds may obscure softer phonemes. Future work in this area will hopefully clarify these issues and provide a firm basis for intervention in both children and adults with AN.

Summary

As our understanding of AN has deepened, it has become apparent that the perceptual consequences of the disorder are quite distinct from those observed for other forms of permanent hearing loss. Where subjects with cochlear-level pathology tend to show impaired spectral- but normal temporal processing, AN listeners typically present with normal frequency resolution but varying degrees of temporal disruption. These fundamental differences have significant consequences for management. While a proportion of individuals (particularly children) with AN can benefit from conventional amplification (Rance et al., 2002), it must be remembered that these devices are not designed to alleviate temporal processing problems[3]. As such, hearing aids can make the speech spectrum audible to children with AN/AD, but it is the degree of temporal distortion that determines whether or not the amplified signal will be useable. Cochlear implantation may in fact, be the best option in many cases (even those with audiograms in the normal to moderate hearing loss range) with severe temporal processing disorder. The development of clinically viable techniques that can assess, in infancy, a child's potential to benefit from hearing aids or electric hearing should therefore be a significant research objective for the future.

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3 Speech processing hearing aids using algorithms that accentuate amplitude and/or temporal cues may be beneficial for listeners with AN/AD (Narne & Vanaja 2008; Zeng et al., 2001).

BARBARA CONE, PHD

The Electrophysiology of Auditory Neuropathy Spectrum Disorder

Introduction

The diagnosis of auditory neuropathy type hearing loss (ANHL) is based upon the presence of one evoked potential (cochlear microphonic, CM) and the absence or abnormality of others (compound nerve action potential, CAP, and auditory brainstem response, ABR). Diagnosis of ANHL with auditory evoked potentials is the easy part. Can auditory evoked potentials (AEPs) be used to differentiate types or sites-of-lesion of auditory neuropathy? Can AEPs be used in the prognosis of speech perception abilities? This review will provide summary of the progress made in these areas. It also aims to suggest areas of research so that the goal of electrophysiological prognosis can be met.

This review of the electrophysiology of ANHL will follow a caudal to rostral organization. Auditory evoked potentials (AEPs), their generator sites and mechanisms, from the cochlea and eighth nerve, from the brainstem, including those evoked by speech and steady-state modulated tones, and from thalamo-cortical areas and pathways, and cortex will be discussed. Both acoustic and electrical stimuli will be considered. An emphasis will be placed on identifying the response parameters of AEPs that are predictive of speech perception outcomes.

Cochlea and eighth nerve AEPs: Cochlear microphonic, summating potential and compound nerve action potential

In an early report of what appears now to be ANHL, Chisin et al. (1979) noted that 9 of 13 children who had hearing loss associated with neonatal hyperbilirubinemia demonstrated a cochlear microphonic (CM) in the absence of an ABR. They suggested that "this is functional evidence of auditory nerve damage in cases of hearing loss following neonatal hyperbilirubinemia, while the hair cells are spared." The association between hyperbilirubinemia and ANHL is now established (Shapiro, 2003). The presence of a scalp-recorded CM and an absent compound VIII nerve action potential (CAP), or ABR is also now established as a diagnostic marker for auditory neuropathy (Berlin et al., 1998; Rance et al., 1999; Rance and Briggs, 2002). The CM remains present in ANHL, even when OAEs are absent, or have deteriorated (Deltenre et al., 1999). Obviously the generator mechanisms for the CM and for OAEs are different, with the latter requiring the cochlear amplifier, and the former does not.

The CM is an extra-cellular, alternating current, receptor potential that follows the acoustic stimulating waveform. It is derived from the currents flowing through outer hair cells (OHCs), as they are polarized and depolarized when transducer channels are opened by stereocilia bending. The CM, recorded from round window or promontory, is generated by OHCs in the basal turn of the cochlea.

The summating potential (SP) is another cochlear receptor potential. The SP is an extra-cellular DC receptor potential, generated by both OHCs and inner HCs. This DC potential may be either positive or negative, depending on the stimulus level and frequency. When measured from differential electrodes within the scala tympani and scala vestibule, the SP is negative at and above the best frequency place and positive at frequencies below best frequency. This negativity corresponds to excitatory depolarization of hair cells. As the stimulus level is increased, the SP becomes negative for frequencies below the best frequency place. There is some evidence that the SP for high frequency, high level stimuli is dominated by electrical current produced by basal-turn IHCs. When CM and SP are evoked by tonal stimuli, the AC component (CM) diminishes as frequency is increased, whereas the DC component (SP) remains. Whereas CM may be seen in a scalp recorded potential, the SP is best obtained using a trans-tympanic electrode, although it can also be measured using a peri-tympanic electrode.

The VIII nerve CAP can be recorded from scalp, peri-, and transtympanic electrodes. Unlike the CM and SP, the CAP is a neural response, generated by spiral ganglion cells, and is the summed effect of mass action potentials proceeding as a volley on the auditory nerve. In response to a click, the CAP is generated by fibers with best frequencies above 4 kHz that are firing synchronously. The CAP is an onset response, and its threshold, latency and amplitude are determined by the frequency and level of the activating stimulus.

Starr et al. (2001) evaluated the amplitude of the CM and SP in 33 patients with auditory neuropathy. These were recorded using scalp electrodes and in response to high level click stimuli. The average pure tone average in this group was 57 dB HL. CMs were evident in 57 ears; in 37 of those ears, TEOAEs were also present. Although the mean CM amplitude was larger in the ears with TEOAE present, the difference in CM amplitude for those with TEOAE absent was not significant. CM amplitudes for the ANHL group were compared to those obtained from normal hearing control subjects. The mean amplitude of CM decreased with age, however, 21 ears of 13 ANHL subjects had abnormally increased CM amplitude in comparison to age-adjusted norms. The subjects with increased CM amplitudes were less than

10 years of age but did not differ from their ANHL counterparts in the degree of pure tone loss. They did not differ in clinical features (risk factors, etiology, presence of other peripheral neuropathy) from those who had CMs within the normal range.

Thirteen ANHL subjects had an ABR wave V in response to high level clicks. There was no difference in CM amplitude between those with preserved wave V and those with absent wave V. SPs were only identified in 50% of all subjects (ANHL or normal hearing controls), and no comparisons could be made on the basis of the limited data set.

The increased CM amplitudes occurred in younger ANHL subjects, only, and there were only 4 control subjects in this age group. Thus, it is unclear whether the increased CMs are reflective of an abnormal process, or whether they were due to sampling bias, as the ANHL group had greater numbers of younger subjects. Young (2000) collected normative data for click-evoked CM amplitude in 26 newborns. The stimuli and recording techniques were similar to those used by Starr et al. (2001). All of the infants tested had normal click-evoked ABRs and distortion product otoacoustic emissions. The CM amplitudes as a function of level are shown in Table 1. These values are similar to those reported as abnormally enlarged in the Starr et al. report.

Table 1. Click-evoked (peak-to-peak) CM amplitudes in neonates.

Level, dB nHL	CM amplitude, uV	s.d.
60	0.12	0.05
70	0.28	0.13
80	0.45	0.45
90	0.57	0.57

CMs could be abnormally enlarged if there were no attenuation of the OHC response by stapedial or MOCB reflexes. The absence of both stapedial reflexes and suppression mediated by the medial olivo-cochlear bundle are hallmarks of ANHL. It is also the case that neonates have immaturity of contralateral suppression, likely due to immaturity of the MOCB reflex. The persistence of "neonatal" CM amplitudes into early childhood may point to an underlying dysfunction of efferent suppression.

An enlarged SP, labeled the "abnormal positive potential" (APP) has been observed in transtympanic (round window) recordings from some children with severe-profound hearing loss (O'Leary et al., 2000). The amplitude of this potential was 2-3 times that of the SP-CAP response in normal hearing subjects and the duration was 3-4 times longer than the typical SP-CAP

complex. The APP was found in 8% (34) of 431 children suspected of having severe-profound hearing loss. None of the children with APP had an ABR wave V when tested with high level clicks. All but two children with APP had pure tone hearing losses in the severe-profound range. The clinical histories of children with APP were typical of others with ANHL, including birth hypoxia, kernicterus, and prematurity. O'Leary and colleagues provided anecdotal outcome data for 26 children who demonstrated the APP. Twelve were reported to have adequate speech and language development with a hearing aid. Another 12 were reported to derive no benefit from amplification, and 8 of these 12 received a cochlear implant. No further outcomes were reported, at that time, for these children.

Santarelli et al. (2008) performed transtympanic electrocochleography in 8 subjects with ANHL and in 16 normally hearing subjects. Pure tone hearing losses were in the mild or moderate range for 6 subjects and in the severe-profound range for 2 subjects. Click stimuli were used to evoke the CM, SP and CAP. CMs were identified in all 16 ANHL ears tested, and were of normal or enlarged amplitude compared to those measured in the control group. CAPs were observed in 5/16 ears. A broad, low amplitude, delayed latency, prolonged duration negative deflection was observed in 7 of the remaining 11 ears. SP could be distinguished from CAP in only 8 of 16 ears; an abnormally large SP observed for one ear. When fast rate click trains were used to evaluate adaptation effects in the SP and CAP, there were 3 types of findings. For two subjects in whom APs could not be defined, adaption did not change the latency, duration or amplitude of the earlier responses (CM or SP). This would suggest that the potentials recorded were pre-neural and interpreted as a disorder localized to the inner hair cells or distal portion of auditory nerve fibers. Three subjects who had SP and CAP distinguished in their recordings demonstrated the same latency and amplitude changes of their potentials that were observed in controls: CAP was attenuated by >60% over the click train, and SP by >20%. These findings suggested that the lesion was post-synaptic, affecting the auditory nerve. Two subjects who did not have an identifiable SP and CAP had potentials that decreased in amplitude during the click-train used to induce adaptation. The amount of amplitude reduction was similar to that seen in control CAP recordings, suggesting a neural site of generation. The investigators suggest that these could be dendritic potentials, reflecting sustained depolarization (and a sustained negative extracellular field) of unmyelinated nerve fibers that have limited ability to generate action potentials at proximal portions of the auditory nerve.

Whereas Santarelli et al. (2008) used an adaptation technique to determine the site-of-lesion, McMahon et al. (2008) used stimuli of different frequencies in their experiments to determine pre- and post-synaptic mechanisms of ANHL. They reasoned that the response (recorded transtympanically) to an 8 kHz toneburst was a receptor potential of IHCs.

They measured SP and CAP in 14 subjects with ANHL. SP and CAP were absent in 2/28 ears. Fifteen ears demonstrated an enlarged SP, with a prolonged latency, of the type described by O'Leary et al. (2000). Eleven ears had a normal SP latency, followed by "broad" (long duration) negative potential, that did not follow the latency shift with level that is characteristic of the normal AP. This was identified as a dendritic potential (DP). The enlarged, prolonged latency SP was interpreted as a pre-synaptic lesion, while a normal SP latency followed by a DP was classified as a post-synaptic lesion. Further discussion of these findings and their implications will be continued below when electrically-evoked ABR (E-ABR) findings are reviewed.

The pre-synaptic disorder, in which enlarged, long latency SPs are found, could be due to disruption of neurotransmitter release, such as demonstrated in mutations of genes that code for otoferlin, a transmembrane protein localized to the IHC ribbon synapse and thought to be necessary for vesicular exocytosis. McMahon et al. (2008) suggest an additional mechanism responsible for the pre-synaptic disorder, that of a static displacement of the operating point of the IHC hair bundle to a closed or silent point. This is similar to the mechanism proposed for endolymphatic hydrops (EH), for which increased SP amplitudes are a hallmark. For EH the enlargement of SP is thought to be due to a biasing of the basilar membrane through fluid displacement into the scala tympani, thus altering the normal electro-mechanical properties of the cochlea, with transduction channels shifted to a "closed" state. It is interesting to note that low frequency hearing loss is characteristic of both EH and ANHL. McMahon and colleaguesl do not, however, provide a mechanism for how the operating point is altered in ANHL.

Transtympanic electrocochleography provides superior resolution of cochlear and VIII nerve potentials compared to those from scalp recordings. The finding of an enlarged summating potential, also identified as the APP, with prolonged latency, is consistent with a receptor or pre-synaptic site-of-lesion, up to the site at which the CAP is generated (i.e., along the unmyelinated process of the auditory nerve fibers). The provision of electrical stimulation to effect a neural response should be effective in these cases. Thus, the enlarged, prolonged latency SP may be prognostic of a good result from cochlear implantation. In contrast, those with a normal SP, but abnormal AP or evidence of DP (indicating abnormal build-up of depolarizing current), likely have a post-synaptic or neural dysfunction affecting more proximal portions of the auditory nerve. In these cases, electrical stimulation of distal processes may not be effective.

Brainstem AEPs: ABR and ASSR

ABR Absent ABRs with the presence of cochlear microphonics (Chisin et al., 1979) and/or normal, mild or moderate pure tone thresholds (Kraus et al., 1984) were the initial indicators of a "neural" or "brainstem" hearing disorder. Chisin and colleagues suggested that the cochlear nucleus could be the site of lesion in deaf children who had a history of hyperbilirubinemia and who had CMs but no ABR. Kraus and colleagues labeled the absence of ABR with less than severe hearing loss as "brainstem dysfunction". Prolonged ABR latencies, reduced amplitudes or abnormal component amplitude ratios, and missing components have often been associated with known neural pathologies such as acoustic schwannomas, brainstem tumors, or deymylinating diseases such as multiple sclerosis. When these types of ABR abnormalities are found in patients with evidence of outer hair cell function (evoked otoacoustic emissions, CMs and/or moderate or milder hearing loss), a disorder of the neural pathway is indicated. In these neural or "retrocochlear" hearing losses, the presence and latency of individual components, and their inter-peak latencies are used to localize the site of disorder, in accordance with the scheme that wave I and II are generated by the auditory nerve, and waves III-V by the pontine and mid-brain auditory nuclei and pathways: cochlear nucleus, superior olive and inferior colliculus (Møller, 2007).

In a majority (70%) of those with auditory neuropathy, acoustically evoked ABRs are absent (Sininger and Oba, 2001). In those that have ABRs, they are reported as grossly abnormal, but there is little to no quantitative information about the abnormalities present. When ABRs are present, only wave V is observed (19% of ANHL patients) or waves III and V (6%). When present, the wave V component is of low amplitude, prolonged latency, and appears as a broad positive-to-negative going potential. These responses in ANHL are similar to what is observed in the normal hearing person in response to clicks at near threshold levels, or are reminiscent of the poorly synchronized ABRs that occur in response to low frequency tonebursts at moderate or lower levels. Those ANHL patients with abnormal ABRs tend to have better pure tone threshold averages than those without ABRs, but the ABR threshold does not bear a correspondence to the audiogram, nor does the pure tone average predict the speech perception abilities. Thus, the acoustically evoked ABR, in combination with tests of cochlear function, can be used to identify the presence of ANHL, but cannot predict the severity of ANHL.

Electrically-evoked ABR (E-ABR) There are now a sizeable cohort of patients with auditory neuropathy who have received a cochlear implant. Several studies have reported E-ABR findings with respect to hearing and speech perception outcomes post-implantation. These studies suggest that E-ABR may be useful in predicting benefit from electrical stimulation.

Gibson and Sanli (2007) performed a retrospective analysis of electrocochleography findings in 39 patients (78 ears) with auditory neuropathy. All of these patients had subsequently received a cochlear

implant, and were tested for an ABR using electrical stimulation. Speech perception abilities were measured after 1 and 2 years of implant use. The results of the electrocochleography and E-ABR tests fell into two groups: A) Large CM and APP, normal E-ABR (N=32) ; B) Large CM and APP, abnormal E-ABR (N=7). The results from these children were compared to a control group of children with severe-profound SNHL who received a cochlear implant. None of the subjects in the control group had enlarged CM or APP (pre-implant), and all had normal E-ABR (post-implant). The patients with ANHL in group A (normal E-ABR) had higher scores on a categorical scale of speech perception abilities than did the control group, with some open set speech perception evident after 2 years of implant use. Group B-ANHL patients had low speech perception abilities in comparison to the SNHL control group and Group A-ANHL patients. After 2 years of implant use, they had achieved detection of speech sounds, discrimination of supra-segmental features of speech and vowel discrimination and recognition. CM amplitude and APP was not prognostic for speech perception outcomes, whereas E-ABR was.

In the McMahon et al. (2008) series of 14 children with ANHL, E-ABRs were completed at the time of implant surgery. E-ABRs were classified as normal, with waves II-V present, absent (essentially a flat line) and "poor morphology", in which the waveform showed some variation with current level, but no distinct peak. The E-ABR and the previous (acoustically evoked) SP and AP results were compared. Those children who exhibited the SP+DP finding, had poor morphology E-ABRs, suggesting that there was a neural synchrony deficit that was not improved with electrical stimulation. Those children who had an enlarged SP with or without residual AP, had normal E-ABRs. Although speech perception outcomes were not provided, there is some overlap of this series and those reported by Gibson and Sanli (2007). Thus, the SP+DP electrocochleography findings, indicative of post-synaptic disorder, are associated with the poor morphology E-ABRs which, in turn, are associated with poorer speech perception outcomes with cochlear implantation. Those with the enlarged SP finding, indicative of pre-synaptic disorder, had normal E-ABRs and good speech perception outcomes.

The threshold, latency and amplitude of E-ABRs from 5 children with ANHL were compared to E-ABRs from 27 children with SNHL (Runge-Samuelson et al., 2008). In 4/5 ANHL patients, E-ABR threshold was within 1 s.d. of thresholds found in children with SNHL, although in 2/5 patients the E-ABR latency at threshold of electrical stimulation was abnormally prolonged. At supra-threshold test levels, ANHL latencies were variable but generally within the range for those with SNHL. E-ABR amplitudes for ANHL were slightly lower than those found in SNHL, and while not quantified, wave V morphology was "broader". The lower amplitude, broad response for ANHL patients suggests poorer neural synchrony, even with electrical stimulation.

Studies in which E-ABR parameters were correlated with speech perception outcomes following cochlear implantation have been carried out in post-lingually deafened adults (Brown et al., 1995; Firszt et al., 2002). These investigations have shown only modest or no correlation between ABR threshold and amplitude-growth slopes and speech perception scores. There is a clue that the absence or abnormality of an E-ABR may indicate poor speech perception outcomes, as Firszt et al noted that the 2 of the 3 poorest speech perception performers in their sample and no identifiable E-ABR, and the third had very low amplitude E-ABRs. This would suggest that the electrical stimulus provided by the implant was insufficient to provide a synchronized neural response, and might reflect a post-synaptic neural disorder, with poor speech perception outcomes.

It is now routine to obtain electrically-evoked CAPs using the cochlear implant electrode as both a stimulus source and recording site. It would be useful to have both E-CAP and E-ABR measures in patients with auditory neuropathy. This would provide the ability to evaluate synchrony at VIII nerve and upper brainstem levels.

ASSR Steady-state amplitude and/or frequency modulated tones and modulated noise can be used to evoke a "steady-state" auditory evoked response. The neural response "follows" the modulation rate, while the cochlear integrity determines the response to the carrier (frequency). The neural generators of the ASSR are dependent upon the modulation rate: at rates of 70 Hz or above, the response is dominated by the response of the auditory brainstem, and at rates of 40 Hz and below, the response is generated at the cortex. (A cortical contribution cannot be ruled-out for higher modulation rates, but this may be developmentally dependent). ASSRs at high modulation rates are primarily used to estimate pure tone threshold in infants and young children, particularly those at risk for hearing loss. During the past 15 years, a number of reports have focused on the correlation between pure tone threshold and ASSR threshold. Quite reasonable threshold predictions are possible, particularly for those with moderate or greater SNHL. This is not the case for those with ANHL. ASSRs may be present, even when ABRs are absent, and this might be perceived as paradoxical, given the shared neural generators. The presence of ASSR with absent ABRs could be due to two reasons. There are differences in the calibration and effective stimulus levels that can be achieved with (modulated) tones versus clicks or tone-pips. Perhaps more compelling is that recording methods for ASSR may allow for the detection of neural responses that are less synchronous than those required for the ABR. That is, EEG energy below 100 Hz is usually filtered out of the ABR, while ASSR uses a high pass filter of 10 Hz or lower. This may allow less well-synchronized onset responses from brainstem sites, but those that are nonetheless able to follow the modulation frequency, to be integrated over the averaging epoch of the recording (usually 1000 ms or more, compared to 10-20 ms for ABR) and result in a response

The absence of ABRs with ASSRs present may be used to raise suspicion that auditory neuropathy exists, although this might also be due to the limitations of the transducer. It is still necessary to obtain a measure of a pre-neural response (EOAE or CM) to confirm the diagnosis. An important finding is that the pure tone sensitivity and ASSR threshold are not correlated in cases of auditory neuropathy. ASSR thresholds are found at 80 dB HL and greater, regardless of pure tone findings, in cases of auditory neuropathy. (Attias et al., 2006; Rance et al., 1998; Rance and Briggs, 2002; Rance et al., 2005). ASSR threshold cannot be used to judge the "severity" of ANHL hearing loss.

 To date, there are no published data on ASSRs at modulation rates lower than 70 Hz, in adults or children with ANHL. At these modulation rates, ASSRs are generated at cortical sites. Cortical evoked potentials have been obtained in children and adults with ANHL (these studies are reviewed below), even when ABRs are absent, so it is possible that ASSRs for low modulation rates would also be present. The time course for maturation of these responses is prolonged, and, to date, there are no published data on ASSRs for slow modulation rates as a function of development in infants and young children. Riquelme and colleagues (2006) obtained 40 Hz ASSRs in newborns, however, in older infants and young children ASSRs at this rate are unstable (Stapells et al., 1988). Until such time as more is known about neurodevelopmental influences on ASSRs, it will not be possible to include them in diagnostic or prognostic test protocols.

ASSRs have been used to estimate temporal processing capabilities in adults (Purcell et al., 2004). ASSRs were obtained from normal hearing adults as the modulation rate was gradually swept from 20 to 600 Hz. The amplitude and presence of the ASSR was compared with several perceptual measures of temporal processing. Overall, there was a correlation between electrophysiologic and perceptual measures. It is plausible that the ASSR could be used to estimate the temporal modulation transfer function, and, in turn, be used to diagnose ANHL. At the very least, this stimulus paradigm tests the auditory system in a dynamic way and its results are related to perceptual measures of temporal processing.

Speech-evoked brainstem responses

Kraus and colleagues have developed a means of assessing brainstem evoked responses to speech sounds (Cunningham et al., 2001; Johnson et al., 2005). A consonant-vowel token (/da/) evokes a complex waveform that resembles the time-domain waveform of the stimulus. This waveform has a transient onset (wave V) and is followed by frequency-following responses to the vowel formants. Children and adults with learning disorders have been shown to have speech-evoked brainstem responses that differ significantly from those with typical learning abilities.

Those with ANHL are unlikely to have an onset response (wave V) to the consonant, and so their results would be abnormal. Would they

demonstrate the frequency-following portion of the response (to the vowel formants)? The frequency-following response (FFR) is generated in the rostral brainstem, likely at the level of the superior olivary complex, by a sub-population of neurons that have exquisite timing capabilities and therefore can follow the timing of individual cycles of a tonal stimulus, at least up to 1500 Hz. It would seem that if neural synchrony were disrupted at the VIII nerve level, that the response of these brainstem neurons would be degraded. Yet, these neurons are encoding a different property of the stimulus than would be evident in response to a click or a toneburst. The presence of an FFR or speech-evoked ABR remains to be tested in those with ANHL.

Cortical AEPs: Middle Latency Response, CAEP, MMN and P300

 Kraus and colleagues (1984) tested for auditory middle latency responses (MLR) in 5 of their 7 patients who had "brainstem dysfunction", that is ABRs absent with no more than a mild-moderate hearing loss. Only one of these subjects had MLRs present, and for only one ear. These subjects were tested during sedated sleep, and except for the 29 -year-old subject, were all under the age of 12 years. The MLR is known to be unstable in young, sleeping children, owing to immaturity of the neural generators, which include the medial geniculate body, reticular nuclei of the thalamus, the auditory radiation and primary auditory cortex.

Auditory evoked potentials from thalamus and cortex may also provide insight into the hearing abilities of those with ANHL. The obligatory components of the CAEP, P1-N1-P2, are generated at the primary auditory cortex, specifically, Heschl's gyrus. There may be contributions from hippocampus, planum temporal and lateral temporal cortex to the P1 component. N1 has multiple generators at the level of auditory cortex, including the superior portion of the temporal lobe; it is these generators that are thought to contribute to the N1's role in reflecting attention to sound arrival. P2 has generators in primary auditory cortex and its association areas, secondary cortex and also, the mesencephalic reticular activating system, but the "center" of activity, when imaged using evoked magnetic fields, is near Heschl's gyrus. Mismatch negativity (MMN), another aspect of obligatory CAEP, has generators in the supra-temporal plane and the lateral posterior temporal gyrus of auditory cortex. The P300 cognitive event-related potential engages activation of the medial geniculate, primary auditory cortex and its belt and parabelt regions, the auditory association cortices, and even motor cortex.

Starr and colleagues' (1996) initial report of 10 patients with auditory neuropathy indicated that of six tested, two had MLRs present (although one had "abnormal" results). Of five subjects in whom cortical auditory evoked potentials (CAEP) were tested, three had responses, although two were noted to be abnormal. Six subjects also had visual evoked potentials

tested and five had normal results. A P300 test paradigm was also used to test three subjects, and all three were reported to have responses present.

Kraus and colleagues (2000) provided a case study of a young adult with ANHL that included comprehensive psychophysical measures and tests of obligatory cortical evoked potentials, P1, N1, P2 and MMN. CAEPs were present although there were latency prolongations in comparison to responses obtained from normal hearing adults. In addition, MMN was present for a /ba-wa/ contrast but not for /da-ga/, and these results were consistent with the subject's psychophysical performance. The CAEPs were sensitive to subtle differences in the patient's auditory abilities; although she had good speech perception in quiet and a normal audiogram, speech perception in noise was very poor.

A combined electrophysiological and psychophysical approach to test temporal abilities was undertaken by Michaelewski et al. (2005). Fourteen subjects with ANHL between the ages of 9 and 60 years of age were tested. Their speech perception abilities ranged from 0 to 100%. Their accuracy and reaction time for noise gaps of 2,5,10, 20 and 50 ms was measured. Obligatory and cognitive CAEP latencies and amplitudes were obtained for stimuli that had gaps of the same duration. In a passive listening condition, only 7/14 subjects had CAEP present, but in the active listening condition, this increased to 11/14 subjects, including all of those who had less than a profound degree of pure tone loss. Gap detection thresholds were poorer than in comparison to a control group, on average, by a factor of 6 (3 vs. 18 ms). The latencies of obligatory and cognitive CAEP components were prolonged relative to the normal control group, however, there was a good correspondence between the gap detection performance measured psychophysically and electrophysiologically. There was also a relationship between gap detection

Table 2 Number and ages of children who had MMN tests

Groups:	ANHL, N	Mean age, months (range)	SNHL, N	Mean age, months (range)
Tones 400 vs. 440 Hz	9	50 (6-92)	12	60 (27-89)
Speech /bad/ vs. /dad/	7	65 (24-92)	11	60 (27-89)

abilities and speech perception abilities, in that the 3 subjects with the highest speech perception scores (>80%) were also able to detect the 5 ms gap. Those with speech perception scores <10% had gap detection thresholds that were 30 ms or greater. In between the two extremes there was a less systematic relationship between speech perception and gap detection abilities.

CAEPs in response to speech tokens, low (400 Hz) and high (3000) Hz tones were obtained in a group (N=18) of children with ANHL and in a comparison group of children with SNHL (Rance et al., 2002). CAEPs were present for tones in 100% of the children with SNHL, and for over 90% in response to the speech tokens, which were presented at levels of at least 20 dB SL. Only 60% of the children with ANHL had CAEPs present, although, when evident, the latency and amplitude of the responses did not differ from their age-matched controls. The children with ANHL who
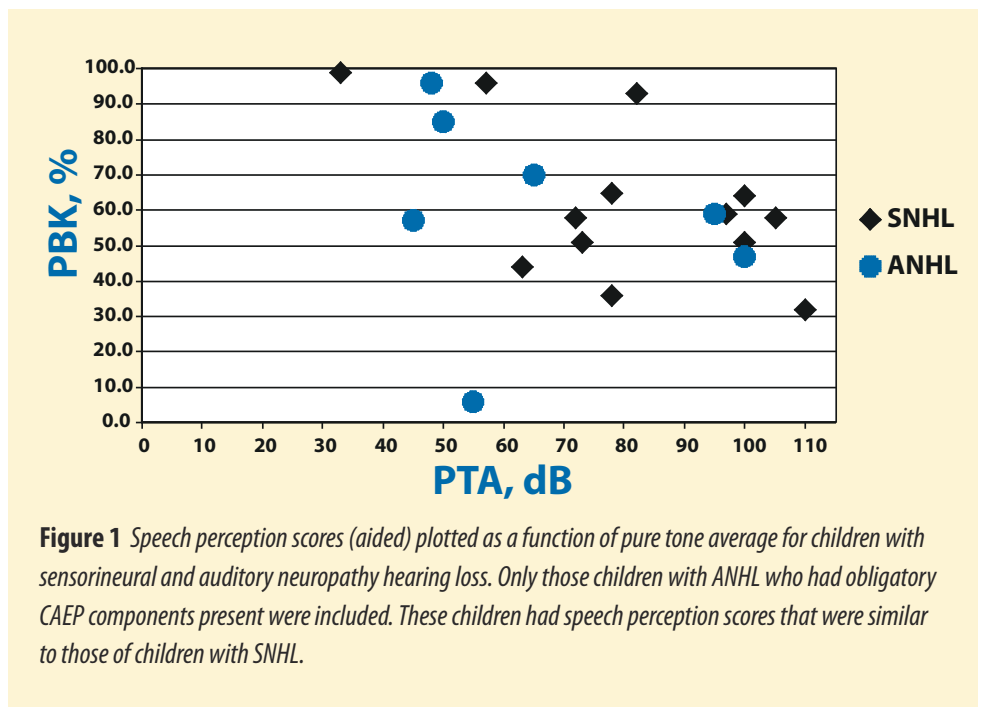

Figure 1 *Speech perception scores (aided) plotted as a function of pure tone average for children with sensorineural and auditory neuropathy hearing loss. Only those children with ANHL who had obligatory CAEP components present were included. These children had speech perception scores that were similar to those of children with SNHL.*

had CAEPs present had significantly higher speech perception scores than those who did not, and they also demonstrated benefit from amplification. The presence of CAEP in children with ANHL appeared to be an indicator that there was a residual neural capacity for speech perception, despite the abnormal input from lower levels of the auditory system. These results raised the possibility that the presence of CAEP in children with ANHL could be used as a prognostic marker.

Mismatch negativity was tested in a sub-group of the children tested in the Rance et al. (2002) study (Cone-Wesson et al., 2003). The hypothesis was that the presence of MMN would be associated with speech perception abilities. Odd-ball stimulus paradigms were used to obtain MMN, contrasting the speech tokens /dad/ vs. /bad/ and low frequency tones 400 Hz vs. 440 Hz. Only those children who had identifiable onset CAEPs (i.e., P1-N1-P2) were included in the data analyses. As well, only those tests for which 60 or more samples of (artifact free) responses to deviants could be obtained were included in the analyses. Table 2 summarizes the characteristics of the ANHL and SNHL groups.

Figure 1 summarizes the (aided) speech perception scores, plotted as a function of the pure tone average, from the children included in the sample. Because only those children who had P1-N1-P2 were included, the speech perception scores of ANHL children are similar to those of SNHL children, and, except for one case, reasonably consistent with the pure tone sensitivity loss. The average speech perception score for the ANHL group was 57% and for the SNHL group, 62%.

MMNs were detected using a statistical criterion. First, the variance of the averaged response to both standard and deviant tokens was calculated. Second, a point-to-point t-test was used to determine the presence of a significant negativity for the response to deviant in comparison to the response from the standard. For an MMN to be judged present, the t-test had to meet a criterion of p<.01 over an epoch of 25 ms.

All children in the SNHL group had MMN for tones, and 10/11 had MMN for the speech token contrast. Only 4/9 children with ANHL had MMN for tones and 2/7 for speech. The average speech perception score for ANHL children with an MMN (for tones and/or speech) was 84%, and for those without an MMN, the average score was 42%. (Speech perception scores were available for only 3 of 4 ANHL children with MMN). In the SNHL group, the average score was 62% and there were 7 children with scores less than 60% who had an MMN for tones.

The mean age of the SNHL group was 10 months older than the ANHL group, however this difference was not statistically significant owing to the high variability in each group. The ages of ANHL children with MMN were 6, 48, 80 and 92 months. In that MMNs were apparent in a 6 month old infant, it is not likely that subject age was a critical factor in whether or not MMN was present. MMNs have been recorded in infants and

children (Morr et al., 2002) even though the CAEP is not fully mature until late teen-age years.

The mean pure tone average in the ANHL group was 63 dB HL, while in the SNHL group it was 78 dB HL. For those ANHL children with MMN
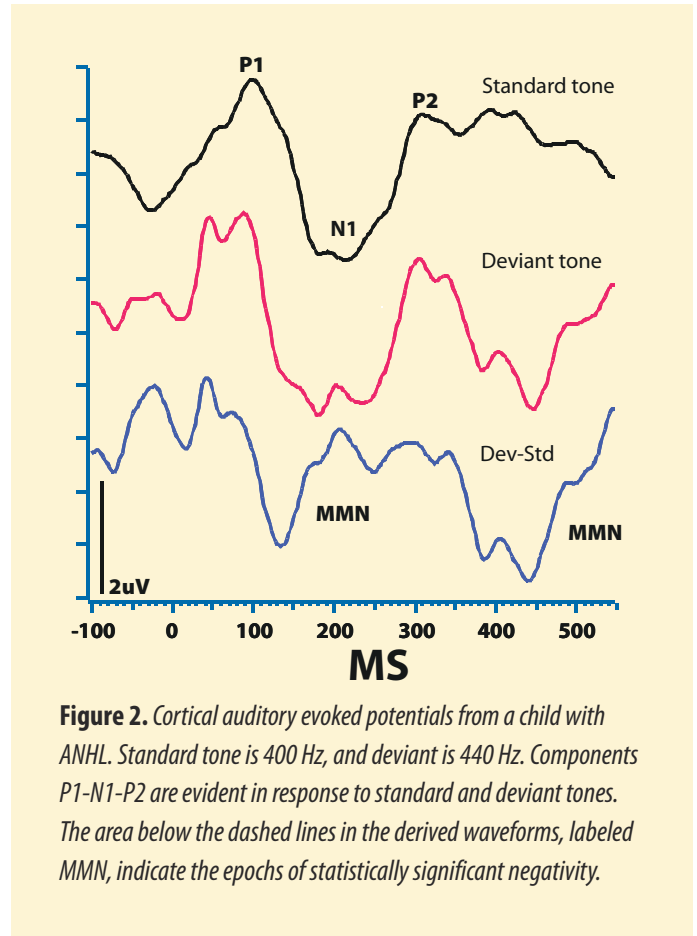

Figure 2. *Cortical auditory evoked potentials from a child with ANHL. Standard tone is 400 Hz, and deviant is 440 Hz. Components P1-N1-P2 are evident in response to standard and deviant tones. The area below the dashed lines in the derived waveforms, labeled MMN, indicate the epochs of statistically significant negativity.*

present, the PTAs ranged from 48-65 dB HL, whereas in the SNHL group there were nine children with PTAs exceeding 65 dB HL who had MMN present. Pure tone sensitivity did not appear to be a limiting factor for MMN in the SNHL group.

The onset and off-set latencies, and duration of MMN were analyzed. There were sometimes two epochs of significant negativity in response to the deviant. There was considerable variability in MMN latency and duration in both the ANHL and SNHL group, with no trends discernable. The first epoch of significant negativity had an onset latency that ranged from 125-175 ms. Examples of the responses to standard and deviant tone tokens, and of the MMN from a child with ANHL are shown in Figure 2.

In summary, MMNs were present in over 90% of children with SNHL, and in less than 50% of those with ANHL. Speech perception scores were higher in the ANHL children with MMNs compared to those who did not

have MMN. Age and amount of pure tone sensitivity loss did not appear to differentiate those who had MMN and those who didn't. The SNHL children had poorer pure tone sensitivity, on average, than those with ANHL, but MMNs were nearly always present. Also, MMNs were present in SNHL children who had poorer speech perception scores than the average of the ANHL group.

The findings appear to support the concept that the presence of obligatory CAEPs, including MMN, are associated with better speech perception outcomes for children with ANHL. The MMN is considered to be an indicator of pre-cognitive acoustic feature discrimination. The presence of MMN in children with ANHL suggests that the neural representation of acoustic features are encoded at cortical levels and enable speech perception.

Cortical evoked potentials can be obtained at suprathreshold levels from passively alert infants, toddlers and children (Wunderlich et al., 2006) and so may be useful in clinical assessment. Tones and speech tokens can be used as stimuli, and, with some speech tokens, it is possible to relate characteristics of the waveform to the acoustic features of speech (Tremblay et al., 2003). These properties were exploited by Pearce et al. (2007) who used CAEP in the management of two infants diagnosed with ANHL. In one case, the presence of CAEP for speech tokens was used to manage amplification decisions. In another, the absence of CAEP for unaided and aided speech contributed to the decision for cochlear implantation. It remains to be determined if CAEPs may be used in threshold estimation for tones and speech in infants and young children. This would be particularly useful for those with ANHL for whom ABR threshold estimation methods are not possible. These methods are currently under investigation at the Arizona Human Electrophysiology and Auditory Development (AHEAD) Lab.

There is only one case report of electrically-evoked CAEP post-implantation in ANHL (Sharma et al., 2005b). Would the provision of electrical stimulation result in a CAEP for those 40% of subjects with ANHL who have absent responses for acoustic stimulation? Is the presence of (electrically-evoked) CAEPs associated with speech perception outcomes? Firszt and colleagues (2002) found that the threshold and amplitude of the MLR but not the CAEP (nor ABR), had a strong and statistically significant correlation with speech perception outcome in a group of post-lingually deafened adults. Three subjects with absent E-MLR and E-CAEP had the lowest speech perception scores (<10%) of the group, however, the speech perception scores of those with E-MLR and E-CAEP ranged from 15- 85%. Because the presence of an acoustically-evoked CAEP has a stronger association with speech perception scores in ANHL than it does for those with SNHL, it is reasonable to suggest that this may be the case for an electrically-evoked MLR and CAEP.

Conclusions and Future Directions

There is still much we need to learn about the sensitivity and specificity of many of our electrophysiological tools, including ABRs for speech sounds, ASSRs at lower modulation rates (and as an assay for the temporal modulation transfer function), and CAEPs in awake, passively alert infants and young children. As well, there is the challenge of the lack of methods that we can use to evaluate psychophysical and speech perception abilities in children younger than 3 years of age. Conventional measures of speech perception require a language age of at least 2.6 years. Visually reinforced infant speech discrimination has been used in the research lab since 1977 (Eilers et al.), but has not yet made it into the clinic. Observer-based psychophysics has taught us much about infant hearing capabilities, but these procedures have not yet been utilized in young infants with hearing loss. It is interesting to note that Trehub and Henderson (1996) showed that gap detection abilities in six- month-old normal hearing infants, tested using a visual reinforcement technique with observer-based psychophysics, were correlated to their language abilities at 18-months- of- age. There are both psychophysical and electrophysiologic methods that can be used to indicate gap detection in young infants. It's time to put them together.

While the challenge of infant psychophysics is no doubt daunting to many, the use of parent questionnaires that systematically query the infant or toddler's use of functional hearing skills is nothing to fear. The Infant-Toddler Meaningful Auditory Integration Scale, IT-MAIS (Zimmerman et al., 2001) and Early Listening Function, ELF (Anderson, 2008) have been used in both clinical and research endeavors to evaluate the effectiveness of aids-to-hearing (cochlear implants and/or hearing aids) in infants. Similarly, the pre-verbal portions of the Early Speech Perception (Moog and Geers, 1990) scales could also be helpful in making systematic observations of hearing abilities related to speech perception. These tools could also be used in ANHL research to quantify the infant's basic functional hearing abilities, to monitor treatment efficacy and to correlate with electrophysiologic results.

A review of the literature on the electrophysiology of auditory neuropathy reveals a focus on the absence of AEPs, rather than on the functional hearing abilities. In some sense, this may have limited progress in treatment. The infant, child or adult with auditory neuropathy does not have CAP or ABR disability, they have a speech perception disability. What is the functional significance of having an acoustically-evoked CAEP for tones or speech? What about a post-implant E-ABR? It is likely that the electrophysiologic profile provided by having CM, SP, CAP, ABR and CAEP for each patient would help to distinguish between the different types of auditory neuropathy. Pre- and post treatment measures, coupled with, at the very least, a measure of speech perception abilities in quiet and noise, would provide a wealth of information to guide diagnosis and prognosis.

Kai Uus, MD, PhD

Identification of Neonates with Auditory Neuropathy Spectrum Disorder

Auditory neuropathy (AN) is a term widely used to label a spectrum of auditory dysfunctions that are typically observed on audiological testing as the presence of normal evoked otoacoustic emissions (OAEs) and/or cochlear microphonic, with an absent or severely abnormal auditory brainstem response (ABR). Though not a new condition per se, it is thanks to the recent routine use of OAEs and ABR in the clinical setting that differentiating this condition from hearing loss associated with outer hair cell damage has become more common. The use of the combination of these two techniques in the context of newborn hearing screening allows us to identify AN virtually at birth. However, in neonates it is currently impossible to distinguish between long-term permanent AN from cases where the transient condition appears to resolve over the early infancy. In order to signify the inclusion of the transient AN in neonatal population the operational term of neonatal auditory dys-synchrony (NAD) will be used based on the results of tests carried out in neonates and very young infants referred by newborn hearing screen.

What is the prevalence of newborn auditory dys-synchrony (NAD)?

In England, each year 600 babies are identified with congenital permanent bilateral moderate or greater hearing loss. Approximately 10% of these present with markers pathognomic for NAD (Uus and Bamford, 2006). In the ever-growing literature the prevalence figures for NAD within the population of children with permanent hearing loss vary widely ranging from 1.8% (Vohr et al., 2000) to 14.6% (Kraus et al., 1984). Prevalence figures for NAD in high risk population are just as varied: 0.2% (Rance et al., 1999; Uus et al., 2006) to 4.0% (Stein et al., 1996). More recently Berg et al. (2005) reported a 24.1% prevalence of NAD from a selected group of special-care infants. The variation is likely to be due to the case definition of NAD as well as characteristics (e.g. age, inclusion or exclusion of unilateral and mild hearing loss) of the underlying population. Prevalence figures for NAD in well-baby population are even more debatable.

How to provide a prognosis for a newborn identified with NAD?

It is not easy to provide a prognosis for an infant identified with NAD , as the patients are likely to go on to display behavioural hearing thresholds ranging from within normal limits to profound hearing loss, and a vast variation in speech perception ability. Furthermore, 24-65% of subjects

identified with NAD (Uus et al., 2006; Psarommatis et al., 2006) appear to have a transient condition. With the current knowledge it is difficult to predict not just the nature and severity of clinical manifestation of NAD but also which infants are likely to show recovery and whether or not the absence/severe abnormality of ABR at birth will resolve without any residual signs either in the auditory system and/or central nervous system in general.

Is transient NAD worth talking about?

In the context of newborn hearing screening talking about transient NAD is inevitable. In case of transient NAD, ABR tracings have been reported to recover by up to as late as two years of age (Madden et al., 2002) and perceptual ability may improve even when ABR remains abnormal. The reported aetiological factors for transient NAD are neuromaturational delay (Psarommatis et al., 2006; Attias et al., 2007), hyperbilirubinemia (Lafreniere et al.,1993; Madden et al., 2002a; Attias et al., 2007), hydrocephalus (Russell et al.,2001), anoxia (Attias et al., 1990; 2007) and, somewhat debatably, metabolic toxic or inflammatory factors (Alexander et al., 1995). In some cases hereditary factors may explain transient NAD. Familial isolated delay of auditory maturation (Neault and Kenna, 2004) as well as presentation as a part of established syndrome such as maple syrup urine disease (Spankovich et al., 2007) have been reported. Transient NAD coexisting alongside delayed visual maturation in the absence of any known risk indicators has been described (Aldosari et al., 2003).

Transient NAD is often labeled 'maturational', implying that it can be explained by normal maturation. This term is not always entirely appropriate, particularly in babies aged over 27 weeks post conception. In a typically developing foetus first signs of myelination are evident by 27 weeks of gestation (Moore and Linthicum, 2001; Moore et al., 1995). Ultrasound imaging has revealed the first behavioral and physiological responses to sound by 25-27 weeks gestational age (Birnholz and Bennecerraf, 1983; Kuhlman et al.,1988). Initial appearance of recordable ABRs in babies born prematurely has been reported at a conceptional age of 27-29 weeks (Starr et al., 1977; Despland and Galambos, 1980; Krumholz et al., 1985; Hafner et al., 1993; Ponton et al., 1993).

Psarommatis et al. (2006) reported that children with lower birth weight were more likely to show electrophysiological improvement and speculated that transient NAD could be present due to the immaturity of

the nervous system. Delayed/altered myelination is often found in premature and/or low birth weight babies. However it is important to emphasize that this population is very diverse consisting of low-risk appropriate-for-age (AGA) neonates, small-for-gestational age (SGA) neonates and neonates with intrauterine growth restriction (IUGR) where several pathological processes are present. The common factors associated with IUGR are (1) maternal factors such as malnutrition, chronic maternal diseases, multiple births; (2) placental pathology, mainly placental vascular damage that may lead to placental insufficiency; (3) intrauterine infections and specific foetal syndromes; (4) non-classified causes such as maternal age, maternal substance abuse, and living at high altitudes.

Because of the diversity of this population it is not surprising that studies investigating the effect of birth weight and prematurity on ABR in these infants have shown conflicting results, reporting both prolonged and shorter latencies, suggesting alterations in myelination but in opposite directions (Kjellmer et al., 1992; Scherjon et al., 1996). That may be caused by not taking into account brain-sparing effect that may have accelerating role in neuromaturation (Sarda et al., 1992; Kim et al., 1995). Hence, it is important not to unreservedly pool together SGA and IUGR infants, let alone AGA infants, but specify the appropriateness of birth weight for gestational age as well as try to establish possible factors for IUGR.

Most importantly, it is clinically necessary to consider whether the abnormality of ABR reflects just delayed maturation of auditory pathways or can it be used as a non-invasive and objective method to assess global neurodevelopment in neonates and young infants. If early ABR proves clinically useful as a marker for neurodevelopmental delay, the present newborn hearing screening programmes could identify infants with needs above and beyond of what the audiology services are currently offering.

To screen or not to screen?
That is NOT the question!

The principles that a screening program should satisfy have been identified in seminal work by Wilson and Junger (1968): (1) the condition sought should be an important health problem in the society concerned; (2) there should be an accepted and effective treatment for the cases identified; (3) facilities for assessment and treatment should be available; (4) there should be a recognizable latent or early symptomatic stage; (5) there should exist a simple predictive test or examination suitable for screening; (6) the test should be acceptable to the population; (7) the natural history of the condition should be understood; (8) there should be an agreed policy on whom to treat as patients; (9) the cost of case-finding (including further assessment and treatment of patients confirmed to have the target condition) should be non-wastefully balanced in relation to possible expenditure on medical care as a whole; (10) case-finding should be a continuing process and not a 'once and for all' project.

While not attempting to dismiss the potential rewards associated with early identification of NAD, it is essential to acknowledge that screening for NAD does not currently meet many of the criteria set by Wilson and Junger (1968). In the newborn hearing screening context the heterogeneity of the condition leads to not only pronounced diagnostic and management challenges but real ethical issues. Having a young baby identified with NAD can potentially be a challenging situation for parents who have to cope with a considerable amount of uncertainty with regard to their child's diagnosis, prognosis, management and choice of communication as professionals are often just as perplexed by the condition as the parents themselves. Finding the most appropriate way to communicate through this persistent uncertainty, ambiguity and contradiction should be as much a priority as is our search for better diagnosis and management.

PATRICIA ROUSH, AUD

Management of Children with Auditory Neuropathy Spectrum Disorder: *Hearing Aids*

The paradoxical findings of absent auditory brainstem responses (ABR) with recordable behavioral responses to sound have been reported for over 25 years (Davis and Hirsch, 1979; Worthington and Peters 1980; Kraus et al., 1984), but the disorder now referred to as "auditory neuropathy/auditory dys-synchrony" (AN/AD) was undiagnosed until advances in audiologic assessment made it possible to conduct differential assessment of sensorineural hearing loss. In the mid-1990's increased attention was brought to these atypical findings by Starr and colleagues who described 10 patients with absent or abnormal ABR accompanied by evidence of normal cochlear outer hair cell function reflected by the presence of a cochlear microphonic and otoacoustic emissions (Starr et al., 1996). Patients ranged in age from 4-49 years and presented without neurologic involvement at the time their hearing disorder was identified; however, eight of the ten patients subsequently developed other peripheral neuropathies including three who were diagnosed with Charcot Marie Tooth disease. The term "auditory neuropathy" (AN) was coined to describe this group of patients whose hearing impairment was attributed to "neuropathy of the auditory nerve" (Starr et al., 1996).

Since the initial report by Starr and colleagues it has become clear that individuals diagnosed with AN are a heterogeneous group even though they may exhibit some common audiologic findings. There are now numerous published reports describing children and adults with a profile that includes absent ABR with otocoustic emissions present and/or a measureable cochlear microphonic and absent middle ear muscle reflexes, but whose varied etiologies and associated conditions suggest differing degrees of impairment and sites of lesion (Rance et al., 1999; Madden et al., 2002a; 2002b). This pattern of test results has been reported in patients with histories of prematurity; neonatal insult; hyperbilirubinemia; perinatal asphyxia; artificial ventilation; and various infectious processes, both bacterial and viral (e.g., mumps and meningitis). Genetic abnormalities have also been described including OTOF, PMP22, MPZ, and NDRGI. In 2006, Buchman and colleagues described a group of children who presented with electrophysiologic responses typical of auditory neuropathy who were subsequently diagnosed by magnetic resonance imaging (MRI) as having cochlear nerve deficiency characterized by absent or small cochlear nerves (Buchman et al., 2006).

Controversy now exists in almost every aspect of the disorder including etiology, site of lesion, and the terminology used to describe the disorder. Rapin and Gravel (2006) argue that the term "auditory neuropathy" is inappropriate unless involvement of the acoustic nerve can be documented. They recommend use of the terms: "sensory hearing loss" for disorders of the hair cells; "auditory neuropathy" for conditions that can be attributed to pathology of spiral ganglion cells and their VIIIth nerve axons; and "central hearing loss" for disorders of the central auditory pathway (cochlear nucleus, inferior colliculus, medical geniculate body or auditory cortex). When comprehensive audiologic and pathologic investigation does not allow differentiation, they recommend the broader description "neural conduction disorder." Others have favored the dual term auditory neuropathy/auditory dys-synchrony (Berlin et al., 2001; Berlin, Morlet and Hood, 2003). A recent report by Gibson and colleagues (2008) notes that imaging combined with genetic and electrophysiological testing should allow identification of various pathological entities according to a specific site of lesion. Hence, they argue that the use of "blanket terms such as auditory neuropathy and auditory dys-synchrony may be more misleading than helpful" (Gibson et al., 2008). Controversy also exists with regard to recommendations for clinical management. Hearing aids and cochlear implants, in particular, have been both promoted and discouraged, often based on minimal clinical evidence.

Clinical Characteristics

The clinical characteristics reported in patients with AN include pure tone thresholds that range from normal to profound; disproportionately poor speech recognition abilities for the degree of hearing loss; difficulty hearing in noise; and impaired temporal processing (Starr et al., 1996; Zeng et al., 1999; Kraus et al., 2000; Rance et al., 2002; 2004; Zeng and Liu, 2006). While some patients diagnosed as having AN exhibit these clinical characteristics, others perform more similarly to patients with "typical" sensorineural hearing loss (Deltenre et al., 1999, Rance, 2005; Rance et al., 1999; 2002; 2007). One perceptual difference reported in both adults and children with AN is difficulty hearing in noise (Gravel and Stapells, 1993; Shallop, 2001). A recent study by Rance and colleagues (2007), however, showed that although children with AN and those with typical sensorineural hearing loss had more difficulty in noise than children with normal hearing, the effects were not consistent across subjects. In fact, some AN children showed relatively good speech perception in noise even at low signal to

noise ratios. Likewise, speech recognition abilities of some children with AN have been shown to be similar to that of their counterparts with typical sensorineural hearing loss (Rance, 2005; Rance et al., 2002; 2004).

Early Management Recommendations

Following the report by Starr and colleagues describing patients with what appeared to be a "neural" hearing loss, several articles and book chapters included recommendations for clinical management, specifically: low gain hearing aids or FM systems; low gain hearing aids in one ear only; or the avoidance of hearing aid use altogether (Sininger, 1995; Berlin, 1996; 1999, Berlin et al., 2002; Berlin, Morlet and Hood, 2003). Zeng et al. (2006) suggested that because temporal processing appears to be affected in patients with AN, amplitude compression should be avoided and linear amplification considered. Also advocated were hearing aids incorporating low-frequency filtering or high frequency transposition (Zeng et al., 2006) and temporal envelope enhancement (Narne and Vanaja, 2008). Further, because the patients described by Starr and colleagues appeared to have pathology of the auditory nerve, it was initially thought that cochlear implantation would be of no benefit, a position reinforced by early reports of poor outcomes following cochlear implantation (Miyamoto et al., 1999; Cone Wesson et al., 2001; Trautwein et al., 2001). More recent evidence has shown that many children with AN benefit from cochlear implantation (Shallop et al., 2001; Buss et al., 2002; Madden et al., 2002a; Mason, De Michelle and Sevens, 2003; Rance and Barker, 2008); however, Rance and colleagues have shown that outcomes are not necessarily predictable. Even for children with AN who benefit from cochlear implantation, performance may be somewhat poorer than is expected for implanted children with "typical" sensorineural hearing loss (Rance and Barker, 2008). Furthermore, in the same study, mean speech recognition scores for the aided AN children were similar to those of the AN children using cochlear implants, however, as Rance points out, the results for aided AN children were biased to some extent because the aided AN children who had initially performed poorly with hearing aids had already been implanted.

Early management recommendations were also offered regarding communication strategies for children with AN. These included recommendations for use of manual communication or cued speech and avoidance of auditory-verbal therapy (Sininger 1995; Berlin et al., 2002).

Support for Hearing Aid Use

Over time, as more young children diagnosed with AN using amplification have been evaluated, reports have shown that hearing aids can provide useful information for some children. Although some require cochlear implantation or a supplemental visual communication system, others with AN appear to derive significant benefit from appropriately fitted hearing aids and auditory-based intervention (Deltenre et al., 1999; Cone Wesson et

al., 2001; Rance et al., 1999; 2002; 2004; 2007). In one of the first systematic studies of hearing aid use in children with AN, Rance et al. (2002) compared unaided and aided speech perception assessments and cortical event-related potentials for a group of 18 children diagnosed with AN, and compared their performance to a group of children with typical sensorineural hearing loss. Their findings indicated that although approximately half of the children with AN showed significant improvement in open-set speech perception with amplification, the other half showed no open-set speech perception ability. Interestingly, cortical evoked potentials were present in all of the children who showed significant open-set speech perception abilities.

The Clinician's Challenge

With the advent of universal hearing screening and increasing survival rates of premature infants, a growing number of young infants with risk factors for this disorder are being diagnosed. These infants present a diagnostic and management challange for pediatric audiologists. For adults and older children, evaluation of thresholds and determination of benefit from a particular hearing technology based on appropriate speech recognition testing, is relatively easy to accomplish. Achieving these goals when working with infants and young children, however, can be considerably more challenging, particularly when they present with AN. Current evidence-based hearing aid fitting protocols for use with infants and young children include measurement of the real ear-to-coupler-differences (RECD) and use of a prescriptive hearing aid fitting method (e.g. DSLv5, NAL). These prescriptive methods require estimates of hearing threshold levels for determining recommended gain and output, to assure that amplified speech is both audible and comfortable. For children with typical sensorineural hearing loss, pure tone thresholds can be estimated from frequency-specific ABR or ASSR evaluation within a few weeks of life; however; for infants with AN, behavioral thresholds cannot be predicted from physiologic measures. Consequently, determination of hearing thresholds is delayed until the infant is developmentally able to perform reliable behavioral assessment using visual reinforcement audiometry (VRA). Most typically developing infants are able to perform this task by 6-9 months of age (Widen et al.,2005) but many infants with AN have disabilities or medical conditions that include developmental delays and, consequently, a lengthier and more complicated process of threshold determination. Furthermore, it is usually not possible to perform speech recognition testing on children below two years of age, making evaluation of progress with amplification difficult even after thresholds have been determined and amplification provided. For all children, benefit from a particular hearing technology will depend on several factors including the child's age at diagnosis and treatment, appropriateness of device fitting, consistency of use, quality of intervention, extent of family involvement,

and other disabilities or medical conditions. In addition, for the child with "typical sensorineural hearing loss" the behavioral pure tone audiogram has prognostic value in the prediction of aided benefit, however; for children with AN it does not. These differences require a management strategy that is similar to that used when determining benefit from amplification versus the need for cochlear implantation in young infants with severe "sensory" hearing loss.

Conclusions

The disorder described as AN is more complicated than originally thought and the patient population is more heterogeneous.

Early recommendations were often based on findings in adults with other peripheral neuropathies. Hearing aids, cochlear implants, and other management strategies were both promoted and discouraged based on relatively low levels of clinical evidence.

There is now a considerable body of clinical evidence that indicates some children with AN can benefit from both hearing aids and cochlear implants, although their performance may differ from that expected in children with typical sensorineural hearing loss.

The evidence regarding clinical management and use of amplification is still limited. Few peer-reviewed studies have been published and the existing literature is based on a relatively small number of children. More research is needed, especially with infants and young children.

Furthermore, studies aimed at evaluating hearing aid outcomes must include evidence-based prescriptive hearing aid fitting methods and real-ear verification methods appropriate for use with infants and children.

Further investigation is needed of alternative hearing aid processing schemes; however, non-traditional strategies need to be evaluated in older children and adults before they are used with infants and young children.

The available clinical evidence does not support withholding audibility from infants with AN. Although audibility does not ensure good speech recognition, lack of audibility is certain to result in poor speech recognition.

The same continuum of multidisciplinary care required for infants with typical sensorineural hearing loss will likely be needed in the management of infants with AN.

Considering the likelihood of varied etiologies, sites of lesion, age of identification, and risks of cognitive/developmental delays, it is unlikely that a single management strategy will apply for all infants and young children who present with this common profile of audiologic test results.

Until the nature and etiology of AN are better understood, and until comprehensive diagnostic tools that allow us to more accurately identify the site of lesion are more widely available for clinical use, generalizations regarding this diverse and heterogeneous group of patients should be avoided.

JON K. SHALLOP, PHD

Management of Children with Auditory Neuropathy Spectrum Disorder: *Cochlear Implants*

Our cochlear implant team is currently responsible for 47 children with auditory neuropathy (AN) who have received a cochlear implant. The majority of the children are unilateral recipients (N=32) and the remaining children have bilateral cochlear implants (N=15). We implanted our first two children with AN in 1998. These two children are siblings and have been identified with mutations of the Otoferlin gene (Varga, 2003). From 1998 to the end of 2007, our cochlear implant surgeons have implanted 413 adults and 210 children.

The proportion of children has increased in recent years and in 2007, 62 adults and 38 children were implanted at Mayo Clinic (Rochester). In our children with cochlear implants, 22% (47/210) were diagnosed with AN. Our overall outcome results for children with AN have been very good as reported in two of our previous publications (Shallop et al., 2001; Peterson et al., 2003) In this paper we will update our outcome data and provide data driven recommendations based on our experience at Mayo Clinic.

There are no published data on how many children with AN have been implanted; however, assuming that there are approximately 110,000 cochlear implant recipients worldwide (Wilson and Dorman, 2007) and that 40% of them are children, then there are at least 44,000 children worldwide with cochlear implants. A conservative estimate of 10% for AN (Uus and Bamford, 2005) can be argued which suggests that more than 4,000 children with cochlear implants worldwide are likely to have AN as a component of their hearing loss etiology.

The Unique Characteristics and Co-morbidities of AN

Children with AN can present with some unique characteristics that may initially be misunderstood by parents and clinicians. In our experience, various physical, sensory or cognitive issues are observed in addition to hearing loss and these may be educationally significant. We have identified 39% of our non-AN children to have at least one significant co-morbidity. Among our population of AN children, we have observed a co-morbidity rate of 54%. The following are the main co-morbidities that we have observed in our AN/AD children: developmental delays, learning

disabilities, ADD, ADHD, autism spectrum disorders, emotional and/or behavioral problems, uncorrected visual problems, blindness, cerebral palsy, motor disorders, apraxia, inner ear malformations, atretic or absent auditory nerve, seizures and various syndromes. Our experiences are probably consistent with other cochlear implant programs. Parents and professionals must be educated and prepared to deal with these issues.

Is the diagnosis correct?

Before a good decision can be made for or against cochlear implantation, it is essential to ensure that the diagnosis is correct and that a cochlear implant is likely to benefit the patient; or would hearing aids be a better option? In some cases, such as cochlear nerve agenesis, hearing aids or a cochlear implant will not benefit the patient and then other options must be considered. The usual diagnostic tests should be utilized including behavioral audiometry, otoacoustic emissions, tympanometry, acoustic reflexes, auditory brainstem responses and a thorough medical assessment. It is important for the surgeons to consider specialized MRI studies in cases of AN to rule out aplasia/agenesis of the cochlear nerve. (Buchman et al., 2006). There is now the possibility of the detection of pre-synaptic vs. post-synaptic etiology differentiation in cases of AN (McMahon et al., 2008). Although there is limited experience with this technique, it may prove to be a method to determine the potential success of a cochlear implant.

Perhaps the most critical component of the cochlear implant evaluation is family education. The families need to be prepared, have realistic expectations and be willing to deal with the new challenges they will face. Hearing aids and cochlear implants do not "fix" the problem of a hearing loss. Parents and extended family have to accept the hearing loss and the process of habilitation that is needed. When families do not understand the implications and how they must provide for their child, the cochlear implant may not be successful, or not optimally successful.

Outcomes for children with cochlear implants

Children with AN usually exhibit pre-operative reduced word and sentence recognition scores that may be atypical for the observed degree of hearing loss. All 47 children implanted at Mayo Clinic had no or very poor open-set speech recognition, without and with appropriate hearing aids. In contrast, Rance and colleagues (2004) reported that about 50% of the 15 AN children they studied showed some significant open set speech recognition. They also
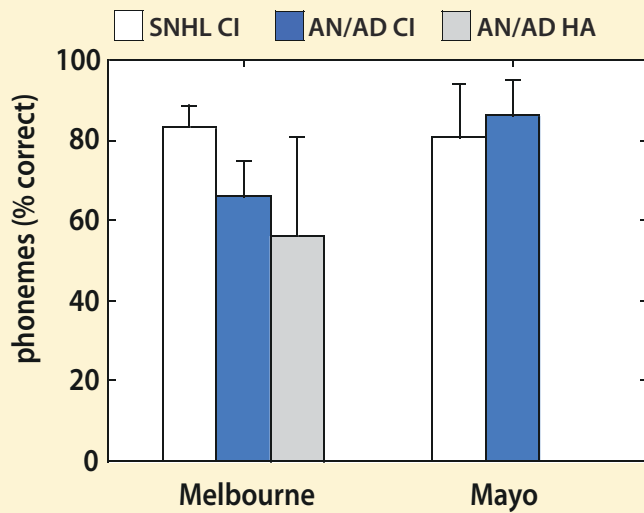
Figure 1. Rance et al. 2007 and Mayo data (unpublished)

showed significant improvement in speech recognition with appropriate amplification, ranging from 40-95% phonemes correct on a children's monosyllabic word test that was administered live voice at conversation level.

Zeng and colleagues (1999) have shown that a group of adults with auditory neuropathy exhibited abnormalities of temporal processing that would have clear implications for speech perception in children. Rance and colleagues (2004) conducted extensive psychophysical and speech perception tests for 15 children diagnosed with AN and 10 children with a non-AN sensorineural hearing loss as well as 10 children with normal hearing. Their major findings were as follows. (1) Normal hearing children all had good speech discrimination scores and could detect small pitch and timing differences. (2) The children with a sensorineural hearing loss had reduced speech discrimination, poor pitch discrimination but normal temporal resolution. (3) Most of the AN children could detect small pitch changes, but could not detect timing differences. The children who had the poorest temporal resolution also had reduced pitch discrimination and the poorest speech discrimination. Children and adults with AN had the most difficulty with temporal processing and fewer problems with pitch

discrimination. In Rance's study, the speech recognition of AN children was worse than their matched peers with non-AN sensorineural hearing loss. However, our experience has been different. We have demonstrated that our AN children do as well as their carefully matched pairs on measures of postoperative speech perception and auditory development. (Shallop et al., 2001; Peterson et al., 2004).

In a recent article, (Rance and Barker, 2008), the Melbourne cochlear implant team reviewed the comparative speech perception (CNC phoneme scores) results in children with AN hearing loss managed with either hearing aids (N=10) or cochlear implants (N=10) as well as children with non AN sensorineural hearing loss (SNHL) who received a cochlear implant (N=10). Their results are displayed in Figure 1 in comparison to a retrospective review of some of our AN children that we have tested so far (N=17) who received a cochlear implant and non AN children (N=26) who also received a cochlear implant. There is a significant main effect of group $(F(3) = 5.01, p = 0.004)$. A post hoc all-pairwise multiple comparison analysis (Tukey) revealed a significant difference between the Melbourne and Mayo data for AN $(q=5.3, p = 0.002)$—but not for SNHL $(q=1.22, p = 0.82)$. Other significant differences found were that the Melbourne implant groups (SNHL vs. AN were significantly different $(q=4.2, p = 0.02)$ and the Mayo SNHL and Melbourne AN groups were significantly different $(q=3.8, p = 0.05)$. All other comparisons were not found to be significant. For analysis purposes, we eliminated 1 of the children from their AN/AD CI group due to very poor performance and an unusual etiology explained in their article.

Summary and recommendations

It is important not to judge speech perception outcomes in any population of children without an understanding of the possibility of sample differences as illustrated in the comparison of our data to the results published by Rance and Barker (2008). Although differences may be statistically significant, there may be other factors that must be considered when making such comparisons between relatively small patient groups. It is clear that some children with AN will benefit from cochlear implantation. The decision to provide an implant for any child requires very careful consideration by the child's family and the cochlear implant team.

CHARLES I. BERLIN, PHD, THIERRY MORLET, PHD, LINDA HOOD, PHD

Management of Individuals with Auditory Neuropathy Spectrum Disorder

Auditory neuropathy/auditory dys-synchrony (AN/AD), renamed by consensus at this meeting as Auditory Neuropathy Spectrum Disorder (ANSD), is the quintessential disorder where many professions working together may serve the patient well. Audiology, speech language pathology, otolaryngology, neurology, early interventionists, and deaf and special education specialists can do their very best work cooperatively from a common knowledge base, assuming they all understand the unique temporally disorganized, static-like, nature of the speech signal perceived by the ANSD patient. (Zeng et al., 1999). Our goal with these patients, as succinctly stated to me by one of my patient's fathers is to "produce a 'literate taxpayer'" in spite of the uncertain auditory impact and trajectory of an abnormal auditory system that shows absent ABR and normal otoacoustic emissions.

This paper is based on what we have learned from following 66 of our own auditory neuropathy patients at Louisiana State University Health Sciences Center (New Orleans), from 11 patients referred from the University of Southern Florida (Tampa), and from 194 patients from other audiologists added to our data base.

In regard to the management of patients with ANSD, we do our worst work by:

1. Being methodologically rigid;

2. Withholding cochlear implantation based on "good audiogram sensitivity which does not meet (outdated) criteria of profound deafness";

3. Failing to evaluate the temporal bone for absent cochleae or absent VIII nerves;

4. Treating some of these patients for years with hearing aids and auditory-verbal techniques as though they were any other patient with a mild-to-moderate sensorineural loss. In the process, we often fail to involve our Speech-Language colleagues to test the patient's current and future language acquisition levels and abilities.

There appears to be an epidemic of these ANSD patients, because we now routinely look for them with otoacoustic emissions and phase reversals of click stimuli during ABR testing, as well as noting paradoxically absent middle ear muscle reflexes in the presence of normal otoacoustic emissions (Berlin et al., 2005; Starr et al.,1996). It is likely that these patients have been with us for years. There may be many, who have been the hearing aid - auditory therapy "failures," that led to cochlear implantation without recognizing the ANSD diagnostic criteria. Other misdiagnosed patients may have been responsible for the "miracles" in which patently deaf children begin to hear and speak by two or three years of age and appear to "outgrow" their congenital difficulties. (Deltenre et al., 1999; Berlin et al., 2001; Attias and Raveh, 2007; Rance, 2005).

In some of these patients the auditory brainstem response (ABR) is never normal; for others, better labeled "auditory immaturity," both the ABR and language acquisition ultimately reach normal values. It is this unpredictability of ANSD, coupled with the superficially conflicting nature of the tests we use that has led to this unique set of problems. The phonologic, acoustic, auditory linguistic and developmental differences between and among patients becomes clearer as we learn more about the pathophysiology and developmental trajectories of this spectrum disorder (Zeng et al.,1999; 2005; Starr et al., 2000; Rance et al., 1999; 2004; Rance and Barker, 2008).

We have collected a large data base of 271 confirmed ANSD adult and child patients evaluated between 1980 and 2005 at the Louisiana State University Medical Center, Kresge Hearing Research Laboratory, Department of Otolaryngology Head and Neck Surgery in New Orleans, LA
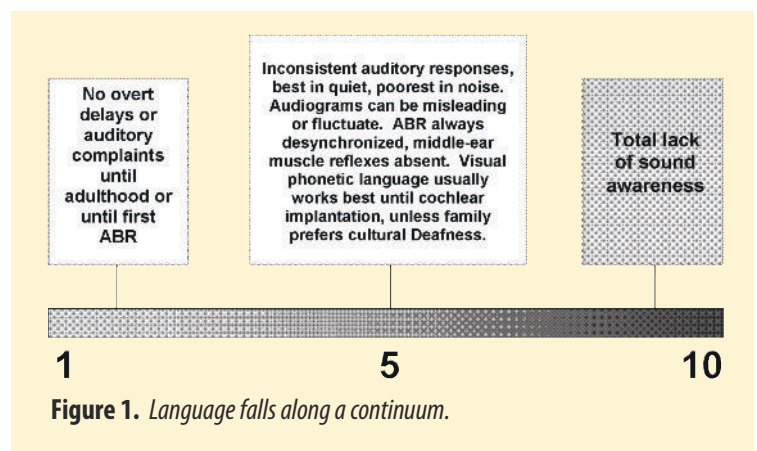

Figure 1. *Language falls along a continuum.*

and from 2006 to 2008 at the University of South Florida, Departments of Communication Sciences and Disorders and Otolaryngology Head and Neck Surgery

Their language falls along a continuum as shown in Figure 1.

Overview of Principles and Sample Patients

Auditory Neuropathy Spectrum Disorder (ANSD) is as much a speech-language and deaf education issue as it is an audiologic and otologic issue. Eighteen of 260 patients (7%) in our data base with ANSD learned language and speech spontaneously — despite never showing synchronous ABR tracings. They were often misdiagnosed as having central auditory disorders because of their characteristically poor hearing abilities in noise and because they show nearly normal audiometric pure tone sensitivity.

There may be many such patients among us, born before universal hearing screening programs were available. These patients would have had no developmental speech, language or hearing complaints. In fact, the first patient (NB) we knowingly saw was a 12-year-old "normal" volunteer who presented for a normative ABR research project. We were surprised to find no ABR, no middle ear reflexes accompanied by a near-normal-hearing audiogram which worsened to what we saw 21 years later (Figure 2). Now
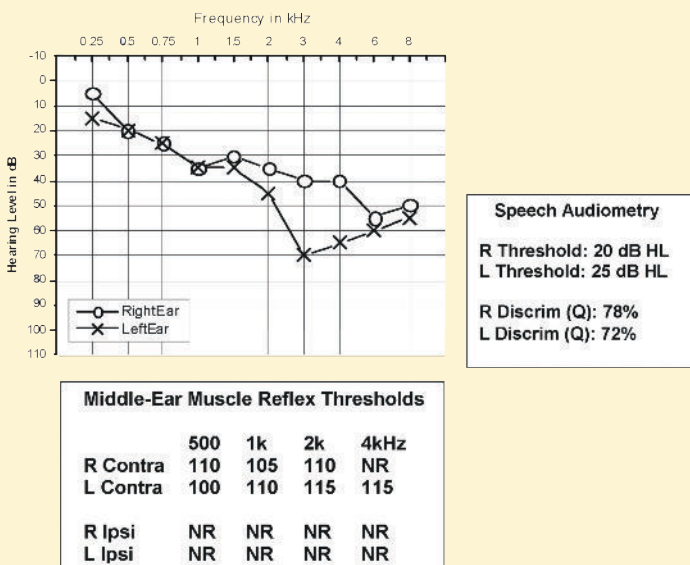

Figure 2.

almost 29 years later, this patient still shows no ABR and still has normal otoacoustic emissions with absent middle ear muscle reflexes. In daily life, he is a successful attorney and complains only of difficulty hearing in noisy

situations and has not responded well to the use of hearing aids. According to the patient, aids had been repeatedly suggested by many professionals who fit whatever audiogram was available using real ear measures and NAL targets.

Behavioral audiograms have not been as valuable for management decisions regarding these patients as similar audiograms are for patients with more common types of hearing loss. For example we have two patients with nearly normal pure tone sensitivity audiograms, one of whom is developing speech and language normally [P0-4)] with no intervention (she is one of the 18 patients mentioned above), and the other who has lost hearing post-lingually. Because of impending blindness
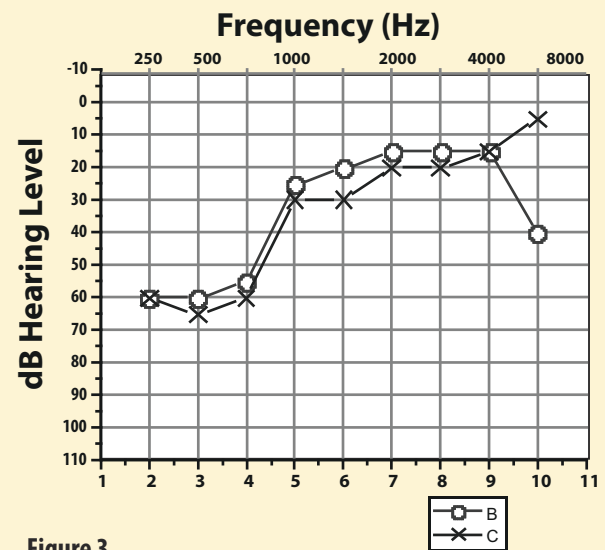

Figure 3.

from Leber's Optic Neuropathy she, received a cochlear implant [EDV-3]. EDV-3 and her similarly afflicted father have both benefited enormously from cochlear implants. Her pre-operative audiogram is shown in Figure 3. Her pre-operative speech recognition in quiet was 8% in one ear and 0% in the other ear. Postoperatively, with the cochlear implant, her discrimination improved to 78% in noise, an exceptional result for any cochlear implant patient regardless of diagnosis and etiology. The pragmatic evidence for usefulness of the implant is this: neither could use a phone before the surgery. Both do so easily now.

Looking back over many years, were hearing aids a good choice?

Hearing aids seemed initially valuable in some patients who showed improved audibility and improved speech discrimination in quiet. But

retrospectively, poor hearing in noise seemed to preclude strong age appropriate language acquisition by auditory eavesdropping in the young children. They seemed to be either falling behind or simply not catching up to their normal hearing peers while they used aids.

All but the first[1] of our 77 patients seen between 1982 and 2008 were offered hearing aids but most did not use them for more than a 30- to 60-day trial period. All of the aids accepted were fit with real ear measures to NAL or DSL criteria whenever possible, although often we could not be sure of the stability and meaningfulness of the audiogram.

Hearing Aid Success based on acquisition of normal language age. Number of Children, birth to 12
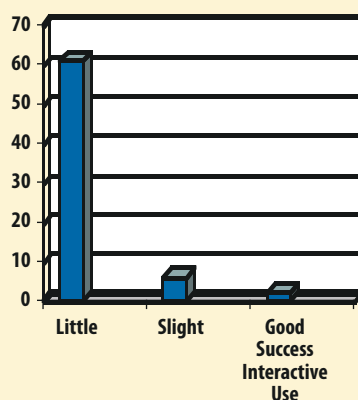

Figure 4. *Hearing Aid Success based on acquisition of normal language age. Number of Children, birth to 12*

In analyzing all the collective data retrospectively from all the clinics who participated, we found that only 5 hearing aid users reached age appropriate language proficiency with this approach. Rance and Barker (2008) and Deltenre et al. (1999) report better hearing aid results based on improved speech discrimination performance in quiet (See also Berlin, with Rance et al, 2007) and at present we have only conjecture based on health care system differences and different criteria for "success" to explain the differences in our observations.

There are data in the literature that hearing aids have generally not been useful in adults with ANSD (Deltenre et al., 1999; Rance, 2005) but are of value in children. These adult ANSD patients seem to have widespread "dead zones" in the cochlea (Moore, 2004). In fact we believe that ANSD may represent a special form of dead zone — perhaps completely or partially penetrating the inner hair cells and auditory nerve fibers (Amatuzzi et al., 2001; Starr et al., 2008).

Why the Discrepancies Regarding Hearing Aid Use?

Our hearing aid data do not match those data reported from other countries where hearing aids and rehabilitation services, as well as cochlear implants, are supplied free of charge to all hearing impaired patients (Deltenre et al., 1999; Rance, 2005; Berlin et al., 2007). Whether the patients in other countries continue to use their hearing aids throughout life and have age-appropriate language is not yet clear. Our data base appears to have the longest time-span (17 years since our first

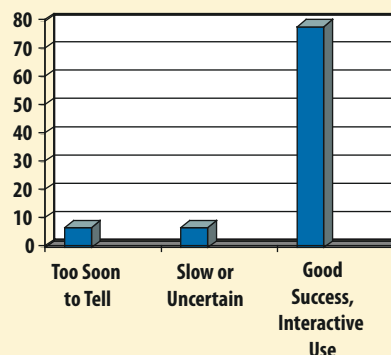### Success with Cochlear Implants

Figure 5. *Success with Cochlear Implants*

hearing aid attempt) over which to make such a determination regarding language performance. Hearing aids have not appeared generally promising to facilitate normal language age development with our 7-10 year overview. Many patients reported in the literature have shown improved audiological sensitivity, and in some cases improved speech discrimination for single syllable words in quiet etc. But the data do not show that the majority of children who showed these audiological improvements in quiet, developed age-appropriate language as measured by speech-language pathologists.

By contrast, cochlear implants have been efficient in supporting age-appropriate language development (Shallop et al., 2001; Peterson et al., 2003).

Because our data base is affected by our health care system and the optional choice of our colleagues to send us the results from their patients, we (Berlin, Morlet and Hood) hope to set up and maintain the data base on an internet site in an easily accessible format. Thus, we plan to control the data base so that only data from bona fide ANSD patients will be included but from all available health care systems, and not just the USA. This

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1 He had a normal pure tone audiogram, no clinical complaints, and was a 12 year old "normal" with no ABR He was a volunteer in an ABR study that was designed to outline normal latencies and amplitudes in various age groups.

should give us a better insight into the long term benefits of various forms of management.

The Importance of Collaboration with Speech-Language Pathologists and Teachers of the Deaf.

Children diagnosed with ANSD need to be able to eavesdrop on language in the same way as normal hearing children do. We cannot predict in advance, from any of our current auditory tests, with the possible exception of late cortical potentials (Sharma et al., 2005a; Rance and Barker, 2008), whether a given child will acquire enough linguistically useful input to learn language spontaneously. Therefore, we recommend that a speech-language pathologist should monitor the child's progress and guide the family as to whether suitable progress is being made during rehabilitation. Our goal is to allow the child to be linguistically and socially interactive during the pre-school years so that they might join normal hearing peers by kindergarten.

How Do We Know the Management is Working?

Insofar as the child makes <u>more</u> than three months progress every quarter, then the therapeutic choices made by the family are salutary. If the child does not make such progress, changes in the treatment, management and habilitation programs should be considered. Thus, we encourage regular monitoring by concerned and informed professionals (i.e., speech-language pathologists, auditory verbal therapists, and/or teachers of the deaf) to assure that suitable progress is being made and management should be adjusted if the child is not progressing as desired.

The Management Theory Our primary responsibility in planning management of the child with ANSD is to <u>do no harm</u>. What has harmed such children in the past according to our data base? Treating the ANSD patient with the immediate application of powerful hearing aids and relentless mouth-covered Auditory-Verbal Therapy (A-VT). This strategy has been especially detrimental when applied to two different types of children. In the first example, a child who has "Auditory Immaturity," will outgrow the disorder by developing a normal ABR and normal hearing audiogram, but may suffer a noise-induced hearing loss secondary to the power hearing aids. The second example is a child whose ANSD dys-synchrony is so severe, even with a mild-to-moderate pure tone audiogram, that mouth-covered AVT is of absolutely no help. A sophisticated AV Therapist should recognize quickly in this child, that traditional mouth-covered A-V methods do not work, and other options with more visual support must be considered. (Personal communication, Karen MacIver-Lux, AVT, has had experience with such children, and has offered this support and advice in our past discussions).

It is important to differentiate ANSD from auditory immaturity (Attias and Raveh, 2007; Psarromatis et al., 2006). In true ANSD, the abnormal ABR never becomes normal. In auditory immaturity, however, the ABR (and concurrent speech and language) become normal over time. At present we have few diagnostic tools to separate the two disorders other than history, watchful waiting and re-testing routinely with ABR during early language training and assessment sessions. Two new physiologic approaches might help separate maturational from true ANSD (McMahon et al., 2008; Walton et al., 2008). Electrical stimulation is also useful if it shows a good response, but hard to evaluate if there is no response. (Runge-Samuelson et al., 2008).

Until these new techniques become more commonly used, we recommend non-invasive, visually supported language training while we wait and watch children with histories of prematurity, hypoxia, hyperbilirubinemia and similar birth dyscrasias. This would do no harm, but help minimize language delay regardless of the child's language trajectory or the parents' therapeutic and educational choices. However in children who have genetic histories such as otoferlin, implants have been most successful in our patients.

Next we must separate genetic etiologies like Otoferlin and MPZ, from neonatal dyscrasias which can cause ANSD. These two categories of etiologies lead to different ANSD recovery courses. Taking a complete birth history and hearing loss pedigree should be helpful because if there is no birth history contribution, and there is a putative genetic cause, early cochlear implantation without waiting for spontaneous recovery has been shown to be quite powerful (see patients BH-1 and JH-1 #s 12 and 13—and TH-1 #14 below). When, and if, a genetic chip becomes available, these ANSD candidate patients should be screened for all known genes. If Otoferlin or Pejvakin or MPZ genes are found, the likelihood is lower that this is a form of auditory immaturity, regardless of birth history. (See http://webh01.ua. ac.be/hhh/). It is essential to perform an MRI with special focus on the VIII nerve as Buchman et al. (2006) have shown a surprising incidence of total absence of the VIII nerve in children with ANSD signs. This absence of the VIII nerve, of course, immediately rules out success with cochlear implants and should be noted as early in the child's development as possible. If the absence is in one ear only, it makes the choice of ear clear. If it is absent in both ears, other routes must be considered including brainstem implants and/or cued speech and/or sign language. (Colletti, 2007).

Protocols for Management Our speech-language team has proposed the following protocol for establishing communication skills baselines. It is recommended to watch and monitor language growth and development every three months. If the child enters the testing

procedure with significant delay in language acquisition, more than three month's progress must be made each quarte r for him to ultimately join his peers academically.

The Speech-Language team has defined and instituted three management protocols, based on the age of the child:

Under Three Years of Age. The basic test battery consists of the *Rossetti Infant Toddler Language Scale (RITLS) or the Preschool Language Scale-4* (PLS-4). The *Developmental Observation Checklist System* may also be administered to infants under six months of age. The choice depends on the maturity of the child. A language sample is also completed. These assessments allow the team to determine the child's present level of language development. An analysis of the child's phonetic inventory, the *Goldman-Fristoe - 2 Test of Articulation* (GFTA -2) or *Structured Photographic Articulation Test-Dudsberry II* (SPAT-D II) are administered to determine the child's speech proficiency.

Three-to-Six Years of Age. The test battery consists of the *Preschool Language Scale (PLS-4), a language sample, and the Receptive One Word Picture Vocabulary Test – R (ROWPVT-R* if the child cannot complete the PLS-4. These assessments allow the team to determine the child's present level of language development. The *Structured Photographic Articulation Test-Dudsberry II* (SPAT-D II), the *Hodson Assessment of Phonological Patterns - third edition* (HAPP-3), or the *Goldman-Fristoe - 2 Test of Articulation* (GFTA -2) are administered to determine speech production proficiency.

Six Years and Older). For children who are of school age, the basic test battery consists of subtests from the *The Woodcock-Johnson III Tests of Cognitive Abilities* (WJ-III ACH) that provide analysis of General Intellectual Ability, Verbal Ability, and Thinking Ability; and the *Woodcock-Johnson III Tests of Achievement Abilities* (WJ-III ACH) that provide analysis of Basic Reading Ability, Oral Language (Std and Ext), Oral Expression, and Listening Comprehension; the *Structured Photographic Articulation Test-Dudsberry II* (SPAT-D II) and a language sample analysis.

Video examples which accompanied the narrative on some of these patients, are available on our web page: http://csd.usf.edu/berlin-russell (no www).

Patients Raised with Cued Speech followed by Cochlear Implants. CASES # 1 AND2. Patient 1 and her brother both have Otoferlin mutations (Varga et al., 2003). At the time of diagnosis in 1996, Otoferlin was not recognized and the children, who were first started with cued speech, were subsequently enrolled in Auditory-Verbal schools with hearing aid to facilitate speech production. The hearing aids were unsuccessful in helping the children learn spoken language. The children,

who had superior receptive language relative to the other auditory-verbal children in their school, were not making the spoken language progress the parents desired. The children both received cochlear implants, although the prevailing wisdom of the time considered ANSD to be a neural deficit which "would not respond positively to cochlear implants." These patients were among many who led us to recommend that "auditory neuropathy" have an added indexed term "auditory dys-synchrony" to prevent the conclusion that there was always neural damage that would not respond to implants in every patient (Berlin et al., 2000). Two and half years following the implants, both were showing superior spoken language and continue to do so now. Both have been implanted bilaterally, educated now in regular schools and taught us that the transition from cued speech to cochlear implants can be a very smooth one. They are patients shared with, and reported by, Shallop et al. (2001) and exemplify the value of cued speech. It served as an excellent tool to maintain normal linguistic, syntactic and phonologic development, while deciding whether or not to implant. Once the implant decision was made by the parents, segue into grammatical spoken language was seamless.

CASE # 3. Patient implanted by 12 months of age, now needs no visual language support

This child's mother opted for pre-linguistic implantation when the child was 8 months of age, but the team's approval allowed for her to be implanted on the day after her first birthday. She had a second implant at 18 months and is mainstreamed in regular school. Her parents describe her now as "indistinguishable from her normal hearing peers." (video on the web page).

CASE # 4. This patient's parents opted only for cued speech, no hearing aids, no implants. Patient KA is 10 years old at the time of this taping and in middle school. Her school, which has supplied a cued speech translator, FM systems, classroom modifications for noise reduction, etc. describes her as a virtually normal child with mild speech problems. Her parents describe her as beginning to recognize that she has trouble hearing. We are strongly considering an implant but have trouble sacrificing her usable hearing. The family continues to consider cochlear implantation, but, as long as her support through Cued Speech continues to help her grow both educationally and linguistically, they do not plan any other interventions. (a brief video on our web page shows her at ages 7 and 10).

Summary. These ANSD children should be treated by a team of specialists including speech-language pathologists, teachers of the deaf, otolaryngologists, pediatricians and neurologists and, where necessary, occupational and physical therapists. About a third of these patients will have concomitant neurologic and motor problems; some will not need

intervention, and others will benefit from cochlear implants, as much, if not more so than hearing aid benefits. We have 5 out of 95 patients in our data base who showed good results with hearing aids in both quiet and noise. However, the common 6-8 dB signal-to-noise ratios provided by hearing aids in everyday life have not allowed the rest of them to eavesdrop on language easily. Many of these patients, but not all, moved on to cochlear implantation. Some ANSD patients stayed with visual language support such as cued speech and used FMs to enhance the signal-to-noise ratio; others chose not to use hearing aids because they

and their teachers and other professionals could observe no differences between conditions when the hearing aid was used or not. Our mantras for proper management of the ANSD patient are as follows:

1. Treat the child's language and speech, and not the audiologic test results acquired in quiet.

2. Do not allow a mild-to-moderate, or even normal, audiogram to disqualify the child from implant consideration if his/her language is not developing normally.

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Hereditary Auditory Neuropathies: From the Genes to the Pathogenesis

Christine Petit

Editorial Note : In the past decade, geneticists have developed a staggering array of new technologies and techniques to advance understanding of hereditary deafness. These techniques have led to the discovery of scores of genes responsible for recessive, dominant, X- linked, Y-linked, and mitochondrial forms of deafness. Notable discoveries during this period include the identification of the genes responsible for the most common cause of recessive deafness (DFNB1, connexin deafness), recognition of genes responsible for "auditory neuropathy" type deafness (DFNB9, otoferlin; and DFNB59, pejvakin), and understanding of the molecular mechanisms underlying the action of these genes.

In the brief paper that follows below, geneticists at the Pasteur Institute in Paris describe the complex and demanding process of identifying the molecular mechanisms of the gene that encodes otoferlin. Through meticulous laboratory methods, these scientists describe how otoferlin contributes to inner hair cell synaptic function. Discoveries of this nature hold the promise of leading to better understanding of the specific mechanism producing hereditary deafness, with the ultimate goal of defining strategies for successful rehabilitative intervention.

In our research studies, we have been working to further identify two genes as the possible cause of two inherited recessive forms of deafness: DFNB9 (Yasunaga et al., 1999) and DFNB59 (Delmaghani et al., 2006) that encode otoferlin and pejvakin, respectively. In both forms of inherited disorder, the clinical criteria to diagnose the auditory neuropathy spectrum disorder are the same association of persistent evoked otoacoustic emission accompanying a severe-to-profound sensorineural hearing loss.

Otoferlin is a predicted transmembrane C2 domain-containing protein (Yasunaga et al., 1999). By immunohistofluorescence study of otoferlin expression in the mouse cochlea, we showed that it is restricted to the sensory hair cells of the cochlea. Its expression in the hair cells parallels their afferent synaptogenesis during development, and is restricted to the inner hair cells (IHCs) in the mature cochlea. By immunoelectron microscopy, we localized otoferlin to the synaptic vesicles tethered to the ribbon and to the presynaptic plasma membrane of the IHCs. Otoferlin binds Ca^{2+} and interacts with syntaxin1 and SNAP25, two proteins of the SNARE complex, in a Ca^{2+}-dependent manner.

In order to address its function in vivo and to understand DFNB9 pathogeny, we generated a knockout mouse model ($Otof^{-/-}$). These mice are profoundly deaf. In vivo electrophysiological studies showed that $Otof^{-/-}$ mice present excitable auditory nerves and functional outer hair cells (OAE preserved), suggestive of a possible IHC defect. By using capacitance measurement, we found that no exocytosis of the readily releasable pool (RRP) of synaptic vesicles and a marginal exocytosis of the slow releasable pool (SRP) could be recorded from IHCs after depolarization in P15 $Otof^{-/-}$ mice, although K+ currents and Ca^{2+} influx were normal. Electron microscopy analysis of the IHCs showed a normal ultrastructure of the IHCs with the exception of their synaptic region, where the architecture and the number of some ribbons of IHC were affected in the $Otof^{-/-}$ mice (although approx. 60% of the synapses remained undistinguishable from the wild-type synapses). At an earlier stage of maturation, P6, a similar drastic reduction of exocytosis could also be recorded, and at that time the architecture and number of ribbons were not affected. Ca^{2+}-flash photolysis did not rescue the exocytosis of the RRP and only rescued 30% of that of the SRP. Based on these results, we proposed that otoferlin is the major Ca^{2+} sensor of the synaptic vesicle-plasma membrane fusion in the IHCs, where it may substitute for the missing synaptotagmin I (Roux et al., 2006).

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