Guidelines for Assessment and Management of Children with Auditory Neuropathy/Dys-synchrony

Linda J. Hood, Ph.D.
Professor, Vanderbilt University, Nashville, Tennessee
Honorary Professor, University of Queensland, Australia

Thierry Morlet, Ph.D.
Head, Auditory Physiology and Psychoacoustics Research Laboratory
Adolphus, duPont Hospital for Children, Wilmington, Delaware

Charles I. Berlin, Ph.D.
Professor, University of South Florida
Former Director, Kresge Hearing Research Laboratory, New Orleans, Louisiana

Patients with outer hair cell responses and absent/abnormal auditory brainstem responses, are classified as having:
- AN: auditory neuropathy*
- AN/AD: auditory neuropathy/dys-synchrony**
- ANSD: auditory neuropathy spectrum disorder***

Possible sites of abnormality:
- Partial or complete loss of inner hair cells, IHC malfunction
- Synaptic juncture of inner hair cells and VIIIth nerve
- Abnormal function of the VIIIth nerve

Ten questions audiologists might ask about AN/AD

- **Assessment**
  - Test strategies and variation (Q1, Q2)
    - With and without ABR
  - Differential diagnosis (Q3, Q4, Q5)
    - EvA, cochlear nerve deficiency, imaging, central APD
    - Neuronomutation
  - Cortical responses and AN/AD (Q6)

- **Management**
  - Amplification and FM systems (Q7)
  - Cochlear implants (Q8)
  - Genetics and AN/AD (Q9)
  - Treating the patient (Q10)

AN/AD Question 1

"What is the best test strategy for accurately identifying AN/AD?"

"What kind of variation can I expect?"

Demographic information

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Number of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-24m</td>
<td>10</td>
</tr>
<tr>
<td>25-48m</td>
<td>20</td>
</tr>
<tr>
<td>4-6y</td>
<td>30</td>
</tr>
<tr>
<td>7-12y</td>
<td>40</td>
</tr>
<tr>
<td>13-18y</td>
<td>50</td>
</tr>
<tr>
<td>19-30y</td>
<td>60</td>
</tr>
<tr>
<td>30+y</td>
<td>70</td>
</tr>
</tbody>
</table>

Gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>55.7</td>
</tr>
<tr>
<td>Female</td>
<td>44.3</td>
</tr>
</tbody>
</table>

*** Auditory neuropathy consensus conference - LinearLayoutManager, 2008. Como, Italy.
OAE test results

Left Ear
- Present: 76%
- Absent: 17%
- Partial/Questionable: 7%

Right Ear
- Present: 75%
- Absent: 16%
- Partial/Questionable: 9%

From Berlin, Hood, Morlet et al., 2010

Auditory Brainstem Response

- The ABR is absent or markedly abnormal
- Recordings appear as:
  - A “flat” ABR with no evidence of any peaks or
  - Poorly synchronized, but later peaks (Wave V) that appear only at high stimulus levels.

Reference: Normal ABR

Efferent Control of the Auditory Periphery

- Middle-ear muscle reflex (MEMR)
  - Controls the stapedius and tensor tympani muscles of the middle ear
  - Absent MEMRs: 90%
  - Abnormal MEMRs: 10% (combination of elevated and absent)

From Berlin, Hood et al., 2010

- Medial olivocochlear reflex (MOCR)
  - Controls portions of the cochlea

From Hood et al., 2003

Patient Variation: A Continuum of AN/AD

No overt delays or auditory complaints until adulthood or until first MEMRs or ABR

Inconsistent auditory responses, can be good in quiet, poor or absent in noise. Audiograms can be misleading or fluctuate. ABR desynchronized, middle ear muscle reflexes absent. Visual phonetic language usually works best until cochlear implantation, unless family prefers cultural Deafness.

Total lack of sound awareness

Question 1: “What is the best test strategy for accurately identifying AN/AD?”

- Physiologic Measures
  - Presence of cochlear responses related to active cochlear mechanisms (OAEs, cochlear microphonics)
    - OAEs affected by middle-ear problems
  - Absent or highly abnormal neural responses
  - Definitive measure is ABR
  - MEMR and MOCR typically affected based on poor afferent input

- Changes over time
  - Stable, fluctuating, progressive (changes in hair cell and/or neural responses)
  - Partial recovery of auditory ability (improved pure tone responses and sound awareness despite continued dysynchrony)
**AN/AD Question 2**

“What can I do to accurately evaluate children with suspected AN/AD if I don’t have access to ABR in my practice?”

**An Audiologic Test Strategy from Kresge Hearing Research Laboratory**

A triage for every new patient:
- Tympanograms
- Ipsilateral and contralateral MEMRs
- Otoacoustic emissions
to quickly and objectively obtain information that guides the remainder of evaluation.

**Audiologic Test Strategy**

- **Tymps abnormal, MEMRs elevated/absent, OAEs absent** - Conductive
- **Tymps normal, MEMRs normal, OAEs normal** - Thresholds < 35 dB HL
- **Tymps normal, MEMRs normal, OAEs absent** - Thresholds most likely between 35-60 dB HL
- **Tymps normal, MEMRs elevated/absent, OAEs absent** - Thresholds > 60 dB HL or neural
- **Tymps normal, MEMRs absent, OAEs present** - Auditory neuropathy/dys-synchrony; neural disorder

**Variation in Detection of Sound**

Audiometric thresholds (n=258 Ears)

**Variation in Discrimination of Sound**

Word recognition in 68 patients age 4 years and older

- **A. 38 of 68 patients** have 0% word recognition in quiet and hearing sensitivity ranging from mild to severe.
- **B. 25 of 68 patients** have variable word recognition in quiet and NO word recognition in noise (+10 signal-to-noise ratio).
- **C. 5 of 68 patients** have good word recognition in quiet and some word recognition in noise, though below normal or SNHL.

**Auditory Neuropathy/Dys-synchrony**

Temporal Processing

Gap

No gap
Question 2: “What can I do to accurately evaluate children with suspected AN/AD if I don’t have access to ABR in my practice?”

- **Physiologic Measures**
  - MEMRs with normal middle ear function
  - Combination of OAEs and MEMRs
    - MEMRs define neural abnormality in presence of normal middle ear function
    - Present OAEs consistent with normal middle ear function

- **Behavioral Measures**
  - Pure tone thresholds are not definitive.
  - Speech recognition in quiet is highly variable; speech recognition in noise typically poorer than found in SNHL.
  - Poorer than expected speech recognition in noise may be a possible indicator to refer for physiologic testing.

AN/AD Question 3

“What other auditory problems might ‘look like’ AN/AD, based on similar test results?”

**Associated Disorders and Differential Diagnosis**

- **Cochlear Nerve Deficiency**

**AI duPont Database**

- 24 children (out of 150+) were identified with MRI evidence of cochlear nerve dysplasia (CND).
- Three were affected bilaterally.
- 60% of unilateral cases occurred on the left side.
- Other inner ear anomalies were found in 50% of patients including all patients with bilateral CND.
- Of the 24 patients tested, more than 75% had an audiometric profile of ANSD (absent MEMR, present OAEs/CM, absent ABR). ANSD feature couldn’t be confirmed in 4 patients.
Imaging studies

- Imaging studies are useful in evaluating hearing loss to diagnose inner ear malformations as well as to check for presence and size of the auditory nerve.
- Absent or hypoplastic auditory nerves are not uncommon (Buchman et al., 2006) and these cases usually resemble ANSD when OHC are present and functioning.
- Audiological management in these patients is problematic because a cochlear implant cannot work when the nerve is absent and might not work well when the nerve is hypoplastic.

An MRI does not give the full picture!

Constellation of findings compatible with cochlear hypoplasia including non-partitioned cochlea, absent visualization of the modiolus, decreased size of the internal auditory canal and absent visualization of cochlear nerve and cochlea aperture.

Associated Disorders and Differential Diagnosis

- Cochlear Nerve Deficiency
- Friedreich Ataxia

Friedreich Ataxia may look like ANSD

- Dys-synchrony
- Gap detection affected as well
- Brain still able to process language for a while (but in good conditions only, i.e., without background noise).
- Dys-synchrony occurs after acquisition of language (ANSD which mostly affects pre-verbal infants).

Associated Disorders and Differential Diagnosis

- Cochlear Nerve Deficiency
- Friedreich Ataxia
- Enlarged Vestibular Aqueduct

Rance et al., 2010

[Graph showing ABR and ASSR responses]
EVA: Definition

- EVA is the most common radiological abnormality seen in children with SNHL: 5-15% of children with SNHL have EVA.
- EVA can be associated with other congenital ear anomalies, such as a hypoplastic cochlea.
- Studies suggest that most children with EVA will develop some degree of hearing loss.
- SNHL onset may occur from birth to adolescence, usually during childhood and may be precipitated by various factors such as head trauma. Hearing loss is often progressive and can fluctuate.
- Vestibular and balance disorders can also be associated.
- Children with an EVA present with a wide variety of audiometric thresholds and physiologic measurements.

ANSD Pattern LE EVA

ANSD Pattern LE EVA

Present CM, Absent ABR

EVA

- Phenotypic expressions associated with EVA are heterogeneous to include the following possibilities:
  - normal hearing
  - total deafness
  - progressive sensorineural hearing loss
  - fluctuating sensorineural hearing loss or sudden sensorineural hearing loss, sometimes subsequent to head trauma.
  - There is not always agreement between OAEs, ABRs, MEMRs, PTA & speech scores.

AN/AD Question 4

“What about neuromaturation?”

“How often does it happen and is there a way to predict this?”
Can we predict which children will have neuromaturation?

- NO!
- Medical review of all children with neuromaturation was inconclusive
- One of the children in the database who had the most risk factors for hearing loss had definite neuromaturation
- Children with neuromaturation had regions of present DPOAEs
- Neuromaturation typically occurs prior to 12 months of age

AN/AD Question 5

“I thought a child had central auditory processing disorder (APD), but it turned out to be AN/AD.”

“How are these two problems similar and different?”

“Is the management different?”

ANSD and CAPD

- Different etiologies
- But both share similarities
- Can be confused unless appropriate testing is used
- Treatment is not the same

Auditory Processing Disorders

- In children, auditory processing disorder (APD) presents as difficulty processing speech despite audiometrically normal hearing.
- Commonly, this difficulty is most pronounced in the presence of competing background noise, which, unfortunately, represents most typical real-world listening situations.
- The causes of (C)APD are not known, and in all likelihood, (C)APD as broadly defined represents a family of auditory processing deficits stemming from multiple causes.

Clinical Presentation

- MEMR present and in the normal range
- OAE present
- Suppression of OAEs present
- Normal ABR (to a click)
- Normal speech in quiet
- Impaired speech in noise
- Deficits related to auditory percepts dependent in temporal cues
Illustrative Case

- Normal birth and medical history
- 11 months: ENT for ear infections
- Babbling at 12 months
- 14 months: 1st set of tubes
- 1st true word at 18 months
- 22 months: 2nd set of tubes
- 3 years: ENT for speech delay. Failed most of her 1st grade classes
- Soundfield audiogram indicated normal hearing thresholds in at least the better ear. Speech therapy recommended
- 7 years: Audiology for CAPD evaluation
- Fluctuations in achievement (good/bad weeks)

ANSD vs APD

<table>
<thead>
<tr>
<th></th>
<th>ANSD</th>
<th>APD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tympanogram</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>MEMR</td>
<td>Abnormal or absent</td>
<td>Present</td>
</tr>
<tr>
<td>OAE</td>
<td>Present or absent (over time)</td>
<td>Present</td>
</tr>
<tr>
<td>ABR</td>
<td>Abnormal or absent</td>
<td>Normal</td>
</tr>
<tr>
<td>Pure-tone thresholds</td>
<td>Normal to severe/profound</td>
<td>Normal</td>
</tr>
<tr>
<td>Word recognition (quiet)</td>
<td>Excellent to poor</td>
<td>Excellent</td>
</tr>
<tr>
<td>Word recognition (noise)</td>
<td>Poor</td>
<td>Fair to poor</td>
</tr>
</tbody>
</table>

Auditory Neuropathy Spectrum Disorder or (C)APD?

- Auditory Neuropathy Spectrum Disorder
  - ABR, MEMR absent
  - Cortical potentials can be present
  - Cochlear implants a management option
- Central APD
  - Peripheral synchrony usually within normal limit
  - ABR, MEMR usually normal
  - Cortical potentials present
  - Cochlear implant not useful

AN/AD Question 6

“What about cortical responses – can they help in figuring out what a child hears and help in planning management?”

Cortical Potentials

- Normal maturation and functioning of auditory cortical areas is a precondition for normal development of speech and oral language skills.
- Disruption of normal maturational processes will result in diminished capacity for speech/language acquisition.
- Cortical potentials are useful in assessing maturation and function of the auditory cortical areas.
Cortical Potentials

- P1 latency seems to be a strong predictor of behavioral outcome.
- Children with ANSD show distinct patterns of central auditory maturation (i.e., different morphology, latency and amplitude of the cortical potentials).
- Cortical potentials can (and should) be used to monitor auditory cortical development before AND during management (can help assess benefit of hearing aids, CI, etc...).

Cortical Potentials

- P1-N1-P2 complex provides information regarding the arrival of sound to the auditory cortex.
- It does not provide information regarding discrimination.
- Other cortical potentials or more complex sounds could/should be considered in evaluating the cortical processing of speech in infants.
AN/AD Question 7

“Do hearing aids and FM systems help?”

“How do I know if hearing aids are helping – or if it’s time to try something else?”

AN/AD Management: Protocols and Outcomes

- Outcomes data are based on three AN/AD patient databases:
  - Kresge Hearing Research Laboratory, Louisiana State University Health Sciences Center, New Orleans, LA
    - Charles Berlin PhD, Linda Hood PhD, Thierry Morlet PhD et al. (1988-2005)
  - Vanderbilt University, Vanderbilt Bill Wilkerson Center, Nashville, TN
    - Linda Hood PhD, Cathi Hayes AuD et al. (2005-present)
  - A.I. DuPont Medical Center/Nemours Children’s Hospital, Wilmington, DE
    - Thierry Morlet PhD et al. (2005-present)

Management of Vanderbilt AN/AD Patients with Hearing Aids

- When should hearing aids be fit?
  - Once frequency specific/ear specific thresholds are obtained through behavioral testing, typically at about 6 months.
  - Fit using pediatric hearing aid fitting protocol (DSL 5.0: Desired Sensation Level).
  - Monitor closely and adjust as needed.

- What if a child cannot perform reliable behavioral testing due to delays in development?
  - Proceed with a conservative hearing aid fitting if the following criteria are met:
    1. Speech evaluation shows delayed receptive and/or expressive language skills.
    2. Parent auditory questionnaire identifies areas of concern.

Outcomes with Amplification

n=198 AN/AD patients from three sites

Kresge Lab (n=85)
- Good benefit = functional interaction, facilitates speech/language development
- Some benefit = some help in language acquisition
- Little benefit = environmental sounds only
- No benefit = no help in communication or speech/language development

Vanderbilt (n=27)
- A.I. DuPont (n=86)

Management of AN/AD: FM Systems

- AN/AD patients generally have very poor ability to understand speech in background noise.
- Vanderbilt AN Patients: FM used with amplification in all patients, but one who uses FM only (normal threshold sensitivity)
- Efferent feedback function (middle-ear and olivocochlear reflexes) is disabled
  - Thought to assist in listening in noise (e.g., Liberman and Guinan, 1998)

AN/AD Question 8

“Who are candidates for cochlear implants?”

“And what are the outcomes?”
Children with ANSD, unsuccessful with amplification, cochlear implant recommended

Lack of responsiveness to sound

Lack of progress in speech/language development

Cochlear implant recommendation
- Lack of progress with amplification
- Continuous delays in speech and language development
- Approximately ⅓ of the Vanderbilt ANSD CI patients have bilateral CIs, by successive or simultaneous implantation.

Outcomes with Cochlear Implants
n=100 AN/AD patients from three sites

Kresge Lab (n=49)
- Successful 78%
- Too soon to tell (recent CI) 15%
- Insufficient information 7%

Vanderbilt (n=20)
- Successful 74%
- Too soon to tell (recent CI) 6%
- Insufficient information 20%

A.I.DuPont (n=31)

Success with cochlear implants has been demonstrated in infants, children and adults with AN/AD.

Post-implant neural response telemetry, EABR, MEMR reflexes are comparable to responses in non-AN/AD implant patients (Shallop et al., 2001)

Inner hair cell, neurotransmitter, synaptic losses could leave neural function intact.

AN patients with conditions associated with VIIIth nerve dysfunction and demyelinating conditions have demonstrated benefit from CI.

Case Study: Detection versus Discrimination in Cochlear Implant Decision-making
- Female, age: 15 years
- Increased listening difficulty, particularly in noise
- Difficulty in school, losing interest
- Vision problems, progressively worsening
  - Optic nerve atrophy
- Other affected family members
  - Autosomal dominant inheritance pattern

Test Results (Age 15 years)

Word Recognition Quiet (40 SL):
- W22*: 8% R / 10% L
- CID Sentences*: 19% R / 36% L

Word Recognition Noise (+10):
- W22*: 0% R / 0% L
- SIN*: 0% R / 0% L

Tymps: Type A R&L
MEMRs: Ipsi and contra absent R&L
Post Cochlear Implant Speech Recognition Results (Age 16 years)

- Hearing In Noise Test (HINT) stimuli at 60 dB HL
  - In quiet: 96%
- CID Everyday Sentences at 60 dB HL
  - In noise: 74% at +10 S/N
  - Pre-implant performance in noise: 0% at +10 S/N

AN/AD Question 9

“Can AN/AD be inherited?”

“What genes are associated with AN/AD?”

Genetics and AN/AD

- Affected siblings or other family members suggests genetic forms of AN/AD
  - Recessive, dominant, and mitochondrial inheritance patterns
- AN/AD can be part of a syndrome or non-syndromic

Candidate Genes (gene name, locus or protein product):
- OTOF
- PJKV
- 13q14-21 (AUNA1)
- Xq23-27.3 (AUNX)
- 12SrRNA (mtDNA)
- SLC19A2
- FXN
- ERG2
- PMP22
- MPZ
- Cx26 (GJB2), Cx29, Cx30 (GJB6), Cx31 (GJB3), Cx32 (GJB1)

Genetics: Non-Syndromic Dominant Auditory Neuropathy

**AUNA1: AUDITORY NEUROPATHY, AUTOSOMAL DOMINANT, 1**
Non-syndromic
Localized to chromosome 13q (13q14-21) by Kim et al. (2004)
Mutation in the DIAPH3 gene on chromosome 13q identified by Schoen et al. (2010)
Clinical Features
- Multigenerational U.S. family of European descent segregating autosomal dominant auditory neuropathy. Hearing loss had an average age of onset of 18.6 years (Kim et al., 2004).
- Benefit from cochlear implants in family members reported by Starr et al., (2004)

Genetics: Non-Syndromic Reccessive Auditory Neuropathy

DFNB9: NON-SYNDROMIC RECESSIVE DEAFNESS
AUNB1: AUDITORY NEUROPATHY, AUTOSOMAL RECESSIVE, 1

DFNB9 and AUNB1 are caused by homozygous or compound heterozygous mutations in the gene encoding otoferlin (OTOF). (Gene map locus: 2p23)

**DFNB9:**
- Lebanese family with nonsyndromic autosomal recessive SNHL. Deafness at birth or before 2 years. Audiology showed profound hearing loss and no ABR. Parents, who were obligate carrier heterozygotes, had normal audiometric tests (Char et al., 1996).

Nonsyndromic Recessive Auditory Neuropathy:
- Varga et al. (2003) defined “nonsyndromic recessive auditory neuropathy” (NSRAN). Varying degrees of hearing loss with poor speech reception out of proportion to the degree of hearing loss. Most not helped by hearing aids, but may be helped by cochlear implants.
- Tekin et al. (2005) reported 3 Turkish sibs, born of consanguineous parents, with NSRAN confirmed by genetic analysis. Severe to profound pre-lingual SNHL. Acoustic middle ear reflexes and ABR absent. DAEs present.

Nonsyndromic Recessive Auditory Neuropathy, Temperature-Sensitive
- Varga et al. (2006) reported 2 sibs with a temperature-sensitive auditory neuropathy phenotype.
- Roux et al., 2006 reported connection of otoferlin to the ribbon synapse.
Genetics and AN/AD
- Otoferlin is expressed at the inner hair cells, possible roles in membrane trafficking and/or IHC synaptic vesicle fusion
- In mice, otoferlin has been localized to IHC associated ribbon synaptic vesicles
- Associated with temperature sensitive AN (e.g., Varga et al., 2003; Marlin et al., 2010; Wang et al., 2010; Matsunaga et al., 2012)
- Multiple mutations; influence of other genes and processes on phenotype not yet known

Genetics and AN/AD
AN/AD occurs as part of a syndrome with various inheritance patterns
- Accompanying other hereditary motor sensory neuropathies - HMSN (e.g., Butinar et al., 1999; Starr et al., 2004)
- Charcot-Marie-Tooth disease
- Friedreich’s ataxia
- AN and optic nerve abnormalities

AN/AD Question 10
“I hear about ‘treating the patient, not the test results’ – what do you mean by that?”

Summary: Evaluation and Management
- Effect, directly or indirectly, is on neural processing of auditory stimuli
  - Physiologic measures are needed to accurately identify AN/AD
  - Important to differentiate detection from discrimination when evaluating outcomes
- Distinguish AN/AD from neuromaturation, EVA, central auditory processing disorders
- Without good auditory input, visual information is critical for auditory communication and speech/language development.
- Many patients benefit from CI, including some with demyelinating conditions; variation is similar to non-AN/AD.
- Follow patients closely and consider the possibility of change in auditory function over time.

Resources
- Listserv for parents and professionals interested in AN/AD AuditoryNeuropathy@yahoogroups.com
- Our Website for information and links: www.kresgelab.com
- Contributions to our database are welcome.