Issues in the Evaluation and Management of Patients with Auditory Neuropathy/Dys-Synchrony

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

Auditory Neuropathy/Dys-synchrony

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***

*** Auditory neuropathy consensus conference. 2008, Como, Italy

Auditory Neuropathy/Dys-synchrony

Possible sites of abnormality:

- Inner hair cells
  - Critical for sound discrimination while OHCs improve detection
- Inner hair cell - VIIIth nerve synapse
- VIIIth nerve

Auditory Neuropathy/Dys-synchrony

Clinical Presentation
- Problems listening in noise, fluctuation, delayed speech/language development

Physiologic Responses
- Hair Cell Responses
  - Present otoacoustic emissions
  - Present cochlear microphonics
- Neural Responses
  - Absent/abnormal auditory brainstem responses
  - Absent/abnormal middle ear muscle reflexes
  - Absent/abnormal MOC reflex/OAE suppression

Behavioral Responses
- Variable audiometric configurations
- Variable but generally poor speech recognition

Auditory Neuropathy/Dys-synchrony

Question for the Audience:
What is the occurrence of AN/AD?

- How many patients with desynchronized ABRs (consistent with severe or profound hearing loss) will have OAEs and/or cochlear microphonics?

  - 1 in 10
  - 1 in 100
  - 1 in 1,000
  - 1 in 10,000

Changes in neural firing patterns can account for reduced or dys-synchronous responses
What is the occurrence of AN/AD?

- About 1 in 10 patients with desynchronized ABRs will have OAEs and/or cochlear microphonics.

- This prediction is based on research from:
  - Of 1000+ children screened in schools for the Deaf, 10-12% had either robust OAEs or evidence of residual OHC function (Berlin, Hood, Morlet, Keats et al., 2000).
  - Of 72 students at schools for hearing-impaired, approximately 10% had either robust OAEs or evidence of OHC responses (Lee et al., 2001).
  - One in 9 infants with permanent hearing loss had cochlear microphonics but no ABR (Rance et al., 1999).
  - Approximately 10% of infants had OAEs and no ABR in the NICHD Newborn Screening Study (Sininger, 2002).

Four Issues

- Variation among patients
- Accurate differential diagnosis
- Changes over time
- Challenges in management

AN/AD Database
Demographic information (n=260)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Male</th>
<th>Female</th>
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<td>0-24m</td>
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<tr>
<td>25-48m</td>
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<td>4-6y</td>
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<td>10</td>
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</tr>
<tr>
<td>30+y</td>
<td>0</td>
<td>100</td>
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</table>

ANOVA Patient Variation:
A Continuum of AN/AD

- No overt delays or auditory complaints until adulthood or until first MEMRs or ABR
- Inconsistent auditory response, best in quiet, patient is in noise; audiograms can be misleading or flat; ABR always desynchronized, middle-ear muscle reflexes absent; visual prompts usually works best until cochlear implantation, unless family prefers cultural deafness.

- Total lack of sound awareness
Variable Characteristics of AN/AD

• Onset: Congenital, later onset, acquired
• Underlying mechanisms: Hair cell, synaptic, neural
• Risk factors in infants
  • Currently unclear, some factors often observed
  • Some infants with AN/AD have no risk factors and come through the well-baby nursery.

Tests Results: Cochlear Function

- Normal otoacoustic emissions
- Present cochlear microphonics
  - Absent/abnormal auditory brainstem responses
  - Absent/elevated middle ear muscle reflexes
  - Absent/abnormal medial olivocochlear reflexes
    - No suppression of otoacoustic emissions
    - No masking level differences
    - Variable audiograms
    - Poor speech recognition

OAE test results

| Left Ear   | Present | 76% |
|           | Absent  | 17% |
|           | Partial/Questionable | 7% |

| Right Ear  | Present | 75% |
|           | Absent  | 16% |
|           | Partial/Questionable | 9% |

Demographic data based on AN/AD Database
From Berth, Houd, Merlet et al., 2010

ABR and Cochlear Microphonics

CM - electrical responses generated in part by the outer hair cells

- Can CM presence alone, without OAEs, be used to diagnose AN/AD?
- CM presence in an ABR trace is normal
Tests Results: Neural Function

- Normal otoacoustic emissions
- Present cochlear microphonics
- Absent/abnormal auditory brainstem responses
- Absent/elevated middle ear muscle reflexes
- Absent/abnormal medial olivocochlear reflexes
- No suppression of otoacoustic emissions
- No masking level differences
- Variable audiograms
- Poor speech recognition

Question for the Audience

Do any patients with auditory neuropathy/dysynchrony have ABRs (some evidence of neural synchrony)?

A. Yes, about 5% of AN/AD patients
B. Yes, about 25% of AN/AD patients
C. No
D. Not sure

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.

Infant Twin 1 - No ABR
Infant Twin 2 - ABR

ABR Considerations: Separating physiologic responses from stimulus artifact

Infant with hydrocephalus and present ipsilateral MEMRs

Auditory Steady-State Response (ASSR)

- Is it possible to use ASSR in the evaluation of ANSD patients?
  - Some reports of phase-locked ASSRs recorded in patients with ANSD who also demonstrate no ABR.
    - But poor agreement with other physiologic test results
    - Poor agreement with behavioral thresholds in adults (Jafari et al., 2009)
  - Suggestion that ASSR may be better able to distinguish severe/profound hearing losses
    - However, reports of responses in patients with no behavioral responses (Jorga et al., 2004; Jang et al., 2004; Picton and John, 2004; Small and Stapells, 2004)
    - Take care at high intensities
Auditory Steady State Response

Responses obtained with different modulation rates have origins in different portions of the auditory system.

- Cortical: Lower modulation rates (40 Hz)
- Subcortical: Higher modulation rates (80-110 Hz)

(e.g., Kuwada et al., 2002)

ASSR

Modulated tones centered on various frequencies are presented. Here, a 2k Hz tone is modulated at 100 Hz.

The EEG response “follows” the modulation envelope of the stimulus.

AN/AD Patient: Click ABR

Efferent Control of the Auditory Periphery

Efferent Reflexes

- Middle-ear muscle reflex (MEMR)
  - Controls the stapedius and tensor tympani muscles of the middle ear
- Medial olivocochlear reflex (MOC)
  - Controls portions of the cochlea

AN/AD Patient: ASSR

Middle Ear Muscle Reflexes

<table>
<thead>
<tr>
<th>Reflexes</th>
<th>Absent MEMRs (all absent)</th>
<th>Abnormal (combination of elevated and absent)</th>
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<tbody>
<tr>
<td>Percent</td>
<td>Bilateral AN/AD</td>
<td>Unilateral AN/AD</td>
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<tr>
<td>Total Absent</td>
<td>90.00</td>
<td>10.00</td>
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Forr Benti, Hood et al., 2010
Test Results: Efferent Neural Function

Middle Ear Muscle Reflexes

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<tr>
<th>Patient</th>
<th>Stimulus Ear</th>
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Efferent Control of the Auditory Periphery

Efferent Reflexes

- Middle-ear muscle reflex (MEMR)
  - Controls the stapedius and tensor tympani muscles of the middle ear

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

Auditory Efferent Reflexes

- The olivocochlear reflex (OAE suppression) is absent in AN/AD patients

Tests Results: Other Measures

- Normal otoacoustic emissions
- Present cochlear microphonics
- Absent/elevated middle ear muscle reflexes
- Absent/abnormal medial olivocochlear reflexes
- No suppression of otoacoustic emissions
- No masking level differences
- Variable audiograms
- Poor speech recognition

Variation in Detection of Sound

Audiometric thresholds (n=258 Ears)

Medial OC fibers are directed to the outer hair cells and most axons cross the midline. (From Berlin, Hood, & Morlet, 2010)
Question for the Audience

- Do any AN/AD patients have word recognition ability that is either “good” or consistent with their pure-tone audiograms?

A. Yes, most patients in quiet & some patients in noise
B. Yes, some patients in quiet & some patients in noise
C. Yes, some patients in quiet & no patients in noise
D. No patients in either quiet or in noise

Word recognition in quiet: SNHL

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).

C. 5 of 68 patients have good word recognition in quiet and some word recognition in noise, though below normal or SNHL.

Kresge AN/AD Database:
Speech recognition ability

Subjects over 4 years of age (n=68)

Measurable word recognition in quiet and in noise (+10 S/N) (n=5)

- Left ear (Quiet): 86.0%
- Right ear (Quiet): 87.2%
- Left ear (Noise): 48.0%
- Right ear (Noise): 64.0%

Auditory Neuropathy/Dys-synchrony

Why is word recognition affected?

Elements of sound: frequency, intensity, time

Psychophysical testing on AN/AD patients:

- Intensity processing
- Frequency processing
- Temporal processing (timing)

- Evidence suggests poor temporal function, dys-synchrony (e.g., Starr et al., 1996; Zeng et al., 1999; Rosner et al., 2004).
Auditory Neuropathy/Dys-synchrony Temporal Processing

Unilateral AN/AD

- Percent
  - Bilateral: 93.8
  - Unilateral: 6.2

- Unilateral Ear Affected:
  - Left Ear: 68.75
  - Right Ear: 31.25

- Patient with unilateral AN/AD

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

“What can I do to accurately evaluate children with suspected AN/AD if I don’t have access to ABR in my practice?”
“What is the best test strategy for accurately identifying AN/AD?”

- Preferred physiologic measures
  - Presence of cochlear responses related to active cochlear mechanisms (OAEs, CM)
  - OAEs affected by middle-ear problems
  - Absent or highly abnormal neural responses
  - Definitive measure is ABR

- If ABR is not available
  - Combination of OAEs and MEMRs

Test Battery Approach

- Physiologic Measures
  - Combination of OAEs and MEMRs
  - MEMRs can define neural abnormality in presence of normal middle ear function and present OAEs

- 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.

The Vanderbilt Protocol

- Otoacoustic emissions (DPOAE)
  - F2 at 2, 3, 4 kHz; 85/35
  - 3 of 3 present with DP amplitude > 0 dB and 6 dB SNR

- Middle-ear testing
  - Tympanogram
  - Middle-ear muscle reflex

- Neural integrity using ABR

- Threshold sensitivity
  - Frequency specific stimuli
  - Air and bone conduction

Audiologic Test Strategy

- The combination of:
  - Tympanograms
  - Bilateral and contralateral MEMRs
  - Otoacoustic emissions

  can provide objective information that guides the remainder of an evaluation.

- If ABR is not available
  - Combination of OAEs and MEMRs

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

AN Patient A

GOOD sound detection and GOOD word recognition
Some children are identified with AN/AD but develop speech and language with little or no intervention, despite no recordable ABRs.

AN/AD Patient “A”

**YOUNGER YEARS**
- Mainstreamed throughout education
- Minimal resource support
- Tried amplification – no benefit
- Some use of FM

**NOW:** 16 years old
- Normal high school classes; excellent student; many extracurricular activities.
- 1 year ago: Expressed difficulty hearing her friends, especially in noise.
- Pure tone thresholds show little change.
- Tried open-fit hearing aids but returned them stating that “using them made it more difficult to hear”.
- **Last week:** More difficulty in school; 7 dB SNR loss re: age-matched peers

**ANSD Issue #2**

**Accurate Differential Diagnosis**

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

**Associated Disorders**

- Includes:
  - Hereditary Motor Sensory Neuropathy (HMSN)
  - Charcot-Marie-Tooth disease (CMT)
  - Friedreich Ataxia (FA)
- Cerebral Palsy
- Optic nerve disorders
- Other neurological disorders

**Differentiating ANSD**

- From cochlear nerve deficiency/agenesis (e.g., Buchman et al.)
- Enlarged vestibular aqueduct (EVA) (Morlet et al.)
- Central APD
- ABR recording technicalities
Associated Disorders and Differential Diagnosis: Cochlear Nerve Deficiency

- Normal
- Absent cochlear nerve
- DPOAEs present bilaterally

Absent or hypoplastic auditory nerves are not uncommon (Buchman et al., 2006).

• Cohort: 24 (of 150) children identified with MRI evidence of cochlear nerve dysplasia (CND).
  - Three bilateral; 21 unilateral.
  - More than 75% had an audiometric profile of AN/AD (absent MEMR, present OAEs/CM, absent ABR).
  - 50% of patients had other inner ear anomalies, including all patients with bilateral CND.
  - Non-partitioned cochlea, decreased size of the internal auditory canal, absent visualization of the cochlear nerve.

• Management: Cochlear implants do not work when the nerve is absent and may not work well when the nerve is hypoplastic (e.g., Teagle et al., 2010).

Associated Disorders and Differential Diagnosis: Enlarged Vestibular Aqueduct

- Most common radiological abnormality in children with SNHL
  - 5-15% of children with SNHL have EVA.
- Can be associated with other congenital ear anomalies, such as a hypoplastic cochlea.
- Most children with EVA will develop some degree of hearing loss.
  - Normal hearing to profound hearing loss
  - Progressive, fluctuating, or sudden SNHL

• SNHL onset: from birth to adolescence, usually during childhood, may be precipitated by various factors, such as head trauma.
• Not always agreement between OAEs, ABRs, MEMRs, PTA and speech recognition.
  - Some EVA patients show test results consistent with AN/AD, others do not.
AN/AD and Central APD

"I thought a child had a 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?"

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

"I thought a child had a 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?"

One of our first patients, referred for CAPD, ultimately determined to have AN/AD

• Male, first seen at age 13 years
• Difficulty in school
• Doesn’t hear instructions
• Doesn’t pay attention
• Sometimes “off in own world”
• In regular classroom, “C student”

Tympanograms: Normal
• Ipsilateral and contralateral instable ear reflexes: Absent
• Word recognition – first test: Quiet 84%, 48%; Noise 0%
• Word recognition – second test: 0% in quiet and noise

AN Patient B

GOOD sound detection and
POOR word recognition

Further evaluations and management

• CT Scan with contrast and MRI: Normal

• Neurological evaluation:
  – Dx of Charcot-Marie-Tooth syndrome
    A group of genetically determined symmetric polyneuropathies with distal muscle weakness, atrophy and sensory nerve involvement; Type 1 – demyelinating changes, limb ataxia

• Management
  – At 13 years
  – Through college
  – Present

Auditory Evoked Potentials

ANSD versus APD

<table>
<thead>
<tr>
<th></th>
<th>ANSD</th>
<th>Central APD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tympanogram</td>
<td>Normal</td>
<td>Normal</td>
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<tr>
<td>Reflexes (MEMR, MOCR)</td>
<td>Absent or elevated/absent</td>
<td>Normal</td>
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<tr>
<td>OAE</td>
<td>Present, may change over time</td>
<td>Present</td>
</tr>
<tr>
<td>ABR</td>
<td>Absent or highly abnormal</td>
<td>Generally normal</td>
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<td>Pure tone thresholds</td>
<td>Normal to severe/profound</td>
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<tr>
<td>Speech in Quiet</td>
<td>Poor to excellent</td>
<td>Generally excellent</td>
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<tr>
<td>Speech in Noise</td>
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<td>Amplification</td>
<td>Benefit in limited cases</td>
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<td>FM</td>
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<tr>
<td>Cochlear Implant</td>
<td>Beneficial</td>
<td>Not recommended</td>
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Infant: Hydrocephalus and present ipsilateral MEMRs

ABR Considerations: Adding waves together to reveal ABR

Infant with hydrocephalus and present ipsilateral MEMRs

ANSD Issue #3
Changes over time

Maturation of the ABR

Distinguishing AN/AD from neuromaturation

Infant ABR at 2 months
Infant ABR at 5 months
At 10 months:
OAEs present
ABR all components present
ABR thresholds normal

AN/AD and Neuromaturation

Hydrops/encephalony.
Exchange Transfusion
Present TEOAEs
Normal thresholds by 7 months

3 wks
4 mos
7 mos

- Cannot predict which children will show changes in ABR related to neuromaturation.
- One of the children who had the most risk factors showed ABR neuromaturation.

Understand data
Hoyes, Hood et al., 2010
Associated Disorders and Differential Diagnosis: Friedreich Ataxia and ANSD

- Hereditary motor sensory neuropathy
- Auditory, motor speech function, mobility
- Onset in second or third decade, progressive
- Dys-synchronous neural response
- Abnormal gap detection
- Difficulty listening in noise
- Auditory characteristics related to ANSD depend on stage and progression

Temperature-Sensitive AN/AD

- Can fluctuate on a daily basis
- Accompanies illness with fever, nervousness, physical activity
- Exhausted after school, frustrated

Word recognition fluctuation with normal thresholds
6-17: L92%; R96%
7-2: L96%; R70%
7-9: L92%; R88%

Recent Audiometric Tests

Tympanograms and MEMRs
- Tubes in both ears
- CT scan: normal

Gap detection thresholds
- Left ear: 13.0 ms
- Right ear: 14.3 ms

Changes over time

- Neuromaturation
- Fluctuation with temperature
- Progression
  - e.g., hereditary motor sensory neuropathies, such as Charcot-Marie-Tooth disease, Friedreich ataxia
- Changes in behavioral responses but not physiologic measures

ANSD Management: Protocols and Outcomes

- Outcomes data from 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)
  - Charles Berlin, PhD, Temple, FL – Consultant (post-2005)
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 (Hood et al., 2003)
  - Thought to assist in listening in noise (e.g., Liberman and Guinan, 1998)

Question for the Audience

- **Cochlear implants have been successful in:**
  A. 5% of AN/AD patients
  B. 25% of AN/AD patients
  C. 50% of AN/AD patients
  D. Over 75% of AN/AD patients

Outcomes with Amplification

- **n=198 AN/AD patients from three sites**
  - Good benefit = functional interaction, facilitates speech/language development
  - Some benefit = some help in language acquisition
  - Little benefit = environmental sound only
  - No benefit = no help in communication or speech/language development

Outcomes with Cochlear Implants

- **n=100 AN/AD patients from three sites**
  - Success = functional interaction, facilitates speech/language development

NOTE: Vanderbilt unsuccessful patient is generalized neural disease, poor neural responses across modalities, abnormal adaptation to sound, resulting in non-use of CI.
AN Patient C

**POOR sound detection and POOR word recognition**

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**AN Patient C**

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**Patient C: Post-operative EABR Electrode 20 @ 12 months**

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**Pre-school: Auditory-oral program**

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**Cochlear Implant Performance**

- Matched 10 AN/AD and 10 non-AN/AD children with cochlear implants
- Threshold and comfort levels comparable
- MAIS (Meaningful Auditory Integration Scale) results comparable

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**Cochlear Implant Performance**

- Matched 35 ANSD and 35 SNHL children with cochlear implants
- No significant difference in word recognition between groups
- 80% of ANSD and 69% of SNHL patients achieved open-set word recognition scores >80%.
  - 32 of 35 ANSD had some open-set word recognition.

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**Why do cochlear implants work?**

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

If neural function is affected, then electrical stimulation may still synchronize remaining neural units better than acoustic stimuli.

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**Why do cochlear implants work?**

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AN Patient D

**GOOD** sound detection and **POOR** word recognition

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Patient D: 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

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OAE and ABR Results
(Age 15 years)

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Audiometric Results
(Age 15 years)

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>250</th>
<th>500</th>
<th>1000</th>
<th>2000</th>
<th>4000</th>
<th>8000</th>
</tr>
</thead>
<tbody>
<tr>
<td>dB Hearing Level</td>
<td>110</td>
<td>100</td>
<td>90</td>
<td>80</td>
<td>70</td>
<td>60</td>
</tr>
</tbody>
</table>

- **SRT:** 20 dB R / 25 dB L
- **WR Quiet (40 SL):**
  - W22*: 8% R / 10% L
  - CID Sentences*: 19% R / 36% L
- **WR Noise (+10):**
  - W22*: 0% R / 0% L
  - SIN*: 0% R / 0% L
- Tymps: Type A R&L
- MEMRs: Ipsi and contra absent R&L

*recorded stimuli

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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

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AN/AD: A Team Approach

- Patient, Family
- Audiologist
- Otologist, Neonatologist, Pediatrician, Neurologist
- Speech-Language Pathologist
- Educator, Early Interventionist (Deaf/Hard of Hearing Educators and Coordinators; Special Educational Services)
- Psychologist, Developmental Specialist, Counselor
Genetics and AN/AD

- Families with multiple affected individuals
  - Recessive, dominant, and mitochondrial inheritance patterns

- Non-syndromic:
  - Dominant (AUNA1)
  - Recessive (AUNB1, NSRAN)

- Part of a syndrome:
  - HMSN (hereditary motor sensory neuropathy); Charcot-Marie-Tooth disease; Friedreich ataxia; AN and optic nerve abnormalities

Candidate Genes (gene name, locus or protein product):
- OTOF
- PUM1
- MIR3
- P2RX6
- GJB3
- GJB6
- Cx26 (GJB2), Cx29, Cx30
- Cx31 (GJB1)
- 12SrRNA
- 13q14-21 (AUNA1)
- OTOF
- SLC19A2
- Xq23-27.3 (AUNX)
- PJVK
- PMP22
- MPZ
- ERG2
- FXN
- DIAPH3
- SLCT9A
- AN/AD

Mapping
- Mapped to a locus on 13q14-q21 (Kim et al., 2010)
- Caused by heterozygous mutation in the DIAPH3 gene on chromosome 13 (Schoen et al., 2010)

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Clinical Features
- Multigenerational family of European descent segregating autosomal dominant auditory neuropathy. Hearing loss had an average age of onset of 18.6 years.

AUTOSOMAL RECESSIVE DEAFNESS (DFNB9) and AUTOSOMAL RECESSIVE AUDITORY NEUROPATHY (AUNB1)

Nonsyndromic recessive deafness caused by homozygous or compound heterozygous mutations in the gene (OTOF) encoding otoferlin (Chromosome 2p23; Varga et al., 2003)

Clinical Features – AUNB1
Nonsyndromic Recessive Auditory Neuropathy (NSRAN, AUNB1) – Clinical Features
- Varying degree of hearing loss with poor speech recognition out of proportion to the degree of hearing loss. Most not helped by hearing aids, but may be helped by cochlear implants. (Varga et al., 2003)
- Three Turkish siblings, born of consanguineous parents, with severe to profound prelingual SNHL. Acoustic middle ear reflexes and ABR absent. OAEs present. (Tekin et al., 2005)

Temperature-Sensitive AN
- Varga et al. (2006) reported 2 siblings with a temperature-sensitive auditory neuropathy phenotype.

Websites
- Hereditary Hearing Loss Homepage
  - G. Van Camp PhD and R. J. Smith MD
  - hereditaryhearingloss.org

- OMIM
  - Online Mendelian Inheritance in Man

Challenges and Progress
- Distinguishing among various forms of AN/AD.
  - Specific characteristics, associated gene mutations, separating hair cell/neural function.
- Characterizing pre- and post-synaptic responses via electrocochleography (ECochG).
- Some children with better speech perception scores demonstrate better cortical responses.
Characterizing Auditory Neuropathy

- Response characterization via trans-tympanic electrocochleography (ECochG)
  - e.g., Santarelli et al., Gibson et al., McMahon et al.
  - Cochlear microphonic (CM), summing potential (SP), compound action potential (CAP)
  - Characterizing pre- and post-synaptic responses
  - Comparison of response thresholds, response amplitude, waveform morphology

Cortical Potentials

- Late latency auditory evoked potentials are useful in assessing cortical auditory function.
- Cortical potentials show promise as a method to objectively characterize speech discrimination ability in young children.
- Cortical potentials can be used to monitor auditory function before AND during management (e.g., benefit of hearing aids, cochlear implants, intervention, etc.).

Characterizing Auditory Neuropathy

Cortical Responses and Discrimination of Sound

- Cortical responses can be present despite no ABR

Issues and Challenges

- Distinguishing among various forms of AN/AD.
  - Specific risk factors
  - Accurate assessment and diagnosis
- Understanding the range of variation within particular forms and how this may influence outcomes.
- Are there characteristics that separate neuromaturation from ANSD?
- How predict who will develop speech/language despite poor neural synchrony?

Cortical responses: Detection of Sound

- Some children with AN/AD show different patterns of central auditory maturation using the P1 response (i.e., different morphology, latency and amplitude of the cortical potentials).

Summary

- Effect, directly or indirectly, is on neural processing of auditory stimuli.
  - Physiologic measures are needed to accurately identify AN/AD
  - Differentiate detection from discrimination when evaluating outcomes
- Patients vary widely in characteristics and management needs.
  - Cochlear and cortical responses, and other sensitive methods, may separate forms of AN/AD and assist in management.
  - Without CI, include visual information for language learning
- Many patients benefit from CI, including some with demyelinating conditions; variation is similar to non-AN/AD patients.
- 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
- Websites for information and links:
  - https://medschool.vanderbilt.edu/hood-lab
  - www.kresgelab.com
- My email: linda.j.hood@vanderbilt.edu
- Contributions to our database are welcome.

Hood 2015

Colleagues at the Kresge Hearing Research Laboratory and the Audiology Clinic, Department of Otolaryngology, Louisiana State University Health Sciences Center, New Orleans, Louisiana, USA

Charles L. Berlin, PhD
Lindsey Rentmeester, AuD
Jennifer Jeanpisay, AuD
Patti St. John, AuD
Harriet Berlin, MS
Leah Ranner, MSc
ML Barchet, MCD
Annette Larmieu, PhD
Lili, MD
Elizabeth Montgomery, AuD
Kelly Rose Mattingly, MA
Pan Wei, MSc
Sanya Tedesco, MCD
Diane Wilensky, MS

The Hood Lab at Vanderbilt University: Mary Edwards AuD, Leawee Roberts AuD, Jessica Creel, Joni Lee BS, Carol Pang BS, Sarah Steele BA, Claire Urness BA, Jordan Racca, BA, Lindsey Rentmeester AuD, Kelsey Hutton AuD, Susan Shing BS, Kristin O’Droho MA, Heather McCadden AuD, Christopher Sparkes-Arm AuD PhD, Bin Mao PhD

The Vanderbilt Auditory Neuropathy Team: Mary Edwards AuD, Cally Hayes AuD, Rene Gifford PhD, Jill Gwinn-Walsh AuD, Andrea Hadley-Williams AuD, Lindsey Rentmeester AuD, Devin McCadden PhD, Gerlina Snell MS, Vic Farnum MD, Dale Tyler MD, Adrian Taylor AuD

Research supported by the NIH-NIDCD, Oberammergau Foundation, Sophie Research Foundation, American Hearing Research Foundation, National Organization for Hearing Research, Meridian Foundation, Akin’s Fund for Hearing Research, Vanderbilt University Development Fund, Vanderbilt Wilkerson Center