Identifying and Managing Children with Auditory Neuropathy/Dys-synchrony

Linda J. Hood, Ph.D.
Professor, Department of Hearing and Speech Sciences
Associate Director for Research, National Center for Childhood Deafness
Vanderbilt University, Nashville, Tennessee

Clinical Goals

- To understand the nature and characteristics of a hearing disorder.
- To obtain sufficient information to provide appropriate management of a hearing disorder.
- To meet the goals of Universal Newborn Hearing Screening programs
  - *Identify and evaluate by 3 months; intervention by 6 months*

Auditory Neuropathy/Dys-synchrony

Patients with outer hair cell responses (OAE, CM) and absent/ abnormal auditory brainstem responses (ABR), are classified as having auditory neuropathy*/auditory dys-synchrony**.

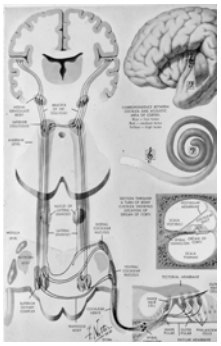
A new recommended name:
*Auditory Neuropathy Spectrum Disorder****

** Starr A, Picton TW, Sininger Y, Hood LJ, Berlin CI. 1996. Auditory neuropathy. Brain, 119:741-753.*
*** Berlin C, Hood L, Rose K. 2001. On renaming auditory neuropathy as auditory dys-synchrony: Implications for a clearer understanding of the underlying mechanisms and management options. Audiology Today 13:15-17.*
**** Auditory neuropathy consensus conference. 2008, Como, Italy*

Auditory Neuropathy/Dys-synchrony

Possible sites of abnormality:

- Inner hair cells
- Inner hair cells - VIIIth nerve synapse
- VIIIth nerve

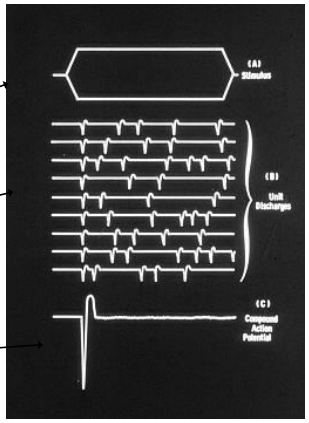


Neural Synchrony

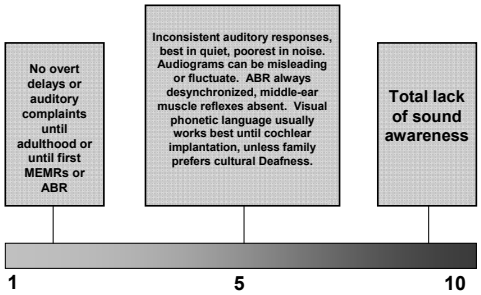
Stimulus Envelope

Single Unit Discharges

Compound Action Potential



Patient Variation: A Continuum of AN/AD



Berlin, Hood, Morlet et al., 2005

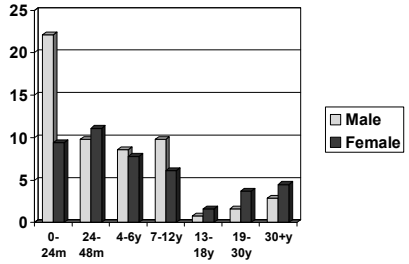
Variable Characteristics of AN/AD

- **Onset: Congenital, later onset, acquired**
- **Underlying mechanisms: Hair cell, synaptic, neural**
- **Risk factors in infants**
  - **Currently unclear, can involve prematurity, hyperbilirubinemia, oxygen deprivation, exchange transfusion**
  - ***Some infants with AN/AD have no risk factors and come through the well-baby nursery.***

Variable Characteristics of AN/AD

- **Genetic patterns: Dominant, recessive, non-syndromic, syndromic, mitochondrial**
- **Changes over time**
  - **Stable, fluctuating, progressive (changes in hair cell and/or neural responses)**
  - **Partial recovery of auditory ability (improved pure tones and sound awareness despite continued dys-synchrony)**
- **Ability to utilize speech information**

Demographic information (n=244)



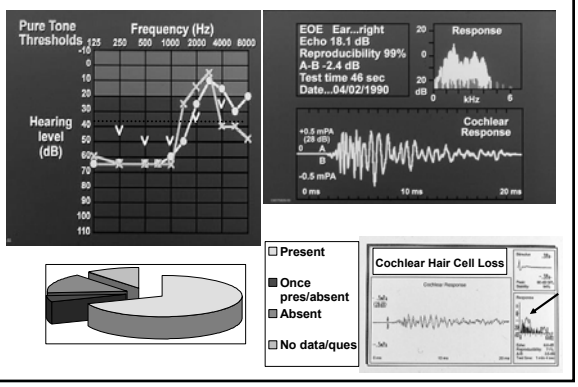
Gender	Number	Percent
Male	136/244	55.7
Female	108/244	44.3

From Berlin, Hood et al., 2008

Tests Results: Hair Cell Function

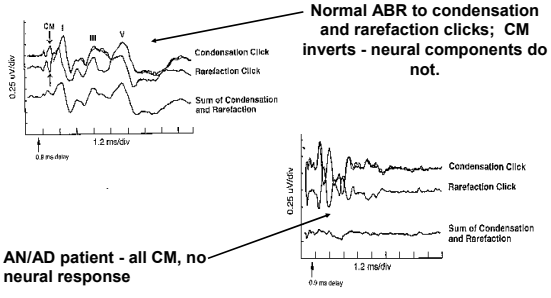
- **Normal otoacoustic emissions**
  (despite abnormal pure tone thresholds)
- **Present cochlear microphonics**
- ***Absent middle ear muscle reflexes***
- ***Absent auditory brainstem responses***
- ***No suppression of otoacoustic emissions***
- ***No masking level differences***
- ***Variable audiograms***
- ***Poor speech recognition***

AN/AD: Otoacoustic Emissions



ABR and Cochlear Microphonics

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



Normal ABR to condensation and rarefaction clicks; CM inverts - neural components do not.

AN/AD patient - all CM, no neural response

Cochlear vs Neural Responses

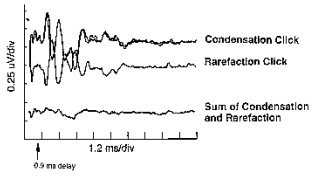
	Cochlear	*Neural*
Latency*	Constant	Increases
Amplitude	Decreases	Decreases
Response*	Inverts	Slight shifts
Masking	Resistant	Decreases

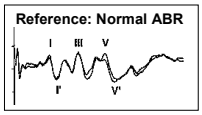
Tests Results: Neural Function

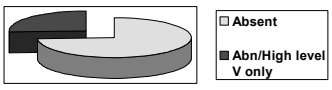
- ***Normal otoacoustic emissions***
- ***Present cochlear microphonics***
- **Absent auditory brainstem responses**
- **Absent middle ear muscle reflexes**
- **No suppression of otoacoustic emissions**
- **No masking level differences**
- ***Variable audiograms***
- ***Poor speech recognition***

Auditory Brainstem Response

Most patients have absent ABRs; some show responses only at high intensities that are low in amplitude.

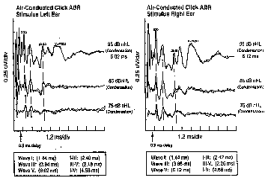


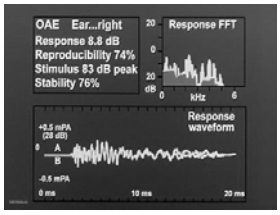


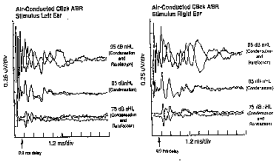


Infant Twin 1:

- **ABR con clicks**
- **ABR con and rar clicks**
- **TEOAEs**

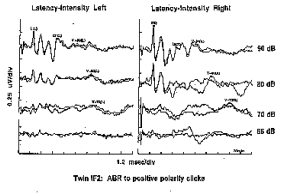




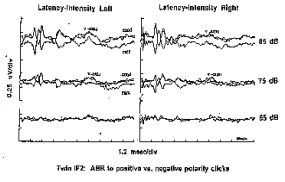


Infant Twin 2 ABR

Condensation clicks

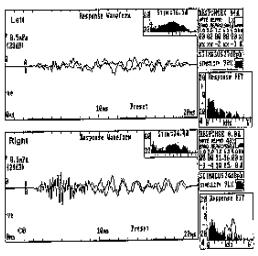


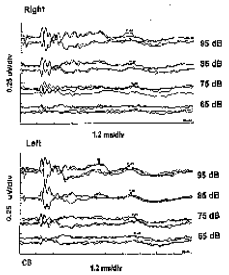
Condensation and rarefaction clicks



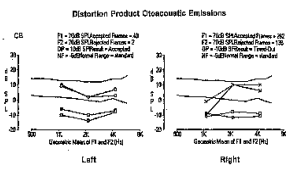
Distinguishing auditory neuropathy/ dys-synchrony from neuromaturation

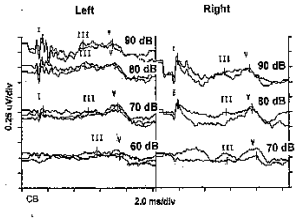
Infant OAEs and ABR 1





Infant OAEs and ABR 2

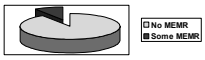




Middle Ear Muscle Reflexes

	Total	Percent
Absent MEMRs (all absent)		
Bilateral AN/AD	127/150	84.67
Unilateral AN/AD	8/150	5.33
Total Absent	**135/150**	**90.00**
Abnormal (combination of elevated and absent)		
Bilateral AN/AD	13/150	8.67
Unilateral AN/AD	2/150	1.33
Total Abnormal	**15/150**	**10.00**

(number of subjects)



From Berlin, Hood et al., 2008

MEMRs in AN/AD Patients

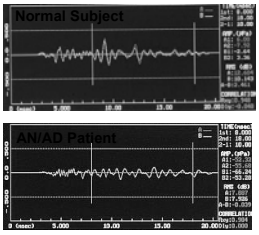
Stimulus Ear:

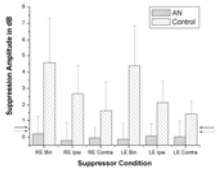
Right	Ipsilateral				Contralateral			
	500	1000	2000	4000	500	1000	2000	4000
Patient								
1	A	A	A	A	110	A	A	A
2	105	105	A	A	105	100	A	A
3	A	A	A	ND	ND	ND	ND	ND
4	A	A	A	A	110	105	110	A
5	ND	ND	ND	ND	100	110	A	A
6	105	105	A	A	A	A	A	A
7	A	A	A	ND	110	110	A	ND
8	95	105	A	A	100	A	A	A
9	100	100	A	A	A	A	A	A
10	100	95	A	A	A	A	A	A
11	105	A	A	A	ND	ND	ND	ND
12	110	110	A	ND	110	110	A	ND
13	A	A	A	A	110	A	A	A
14	90	85	A	A	90	85	A	A
15	ND	ND	ND	ND	115	A	A	A

From Berlin, Hood, Morlet et al., 2005

Auditory Efferent Reflexes

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





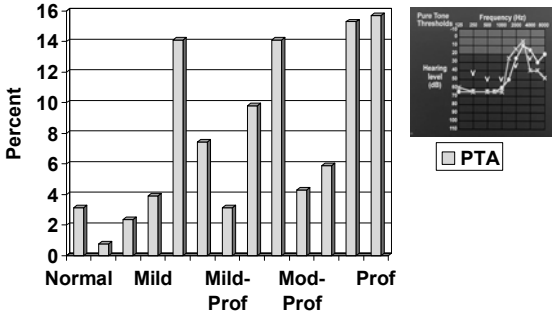
Hood et al., 2003

Test Results: Other Measures

- ***Normal otoacoustic emissions***
- ***Present cochlear microphonics***
- ***Absent auditory brainstem responses***
- ***Absent middle ear muscle reflexes***
- ***No suppression of otoacoustic emissions***
- ***No masking level differences***
- **Variable audiometric configurations**
- **Poor speech recognition (most often)**

Audiometric test results

(n=*153 Ss)*



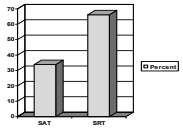
From Berlin, Hood et al., 2008

Speech audiometric test results

(based on data from 71 subjects over 4 years old)

	Percent
Speech Reception or Awareness Thresholds	
Speech Awareness (SAT)	33.8
Speech Reception (SRT)*	66.2

SRTs were typically obtained using a very limited set of spondees.



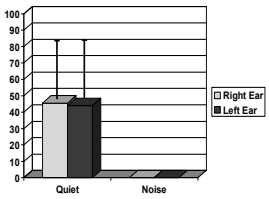
From Berlin, Hood et al., 2008

Kresge AN/AD Database: Speech recognition ability

Subset of 71 patients aged 4 years and older

Measurable word recognition in quiet: 27
- **Average maximum word recognition 45%**

Measurable word recognition in noise: 0%



Speech audiometric test results

(based on data from 95 subjects)

Subjects with measurable word recognition in Quiet and Noise (over 4 years of age) = 5 subjects

Left ear (Quiet)	Mean: 86.0%	[SD: 12.8%]
Right ear (Quiet)	Mean: 87.2%	[SD: 8.7%]
Left ear (Noise**)	Mean: 48.0%	[SD: 15.8%]
Right ear (Noise**)	Mean: 64.0%	[SD: 22.1%]

*** Speech in noise testing was typically at a +10 signal-to-noise ratio.*

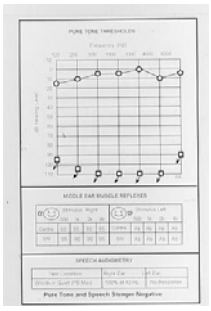
From Berlin, Hood et al., 2008

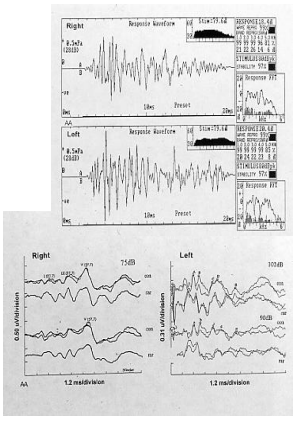
Auditory Neuropathy/Dys-synchrony

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., 1998; Zeng et al., 2000).***
- ***What AN may sound like - Dr. F-G Zeng***

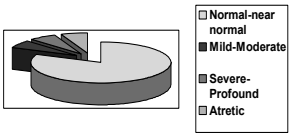
Unilateral Auditory Neuropathy





Kresge AN/AD Database: Unilateral AN/AD

- **Hearing in opposite (non-neuropathy) ear**
  - **Normal or near normal = 13**
  - **Mild-moderate hearing loss = 1**
  - **Severe-profound hearing loss = 1**
  - **Atretic =1**



Patient History and Risk Factors

Subjects aged 0-18 years (n=175/260)

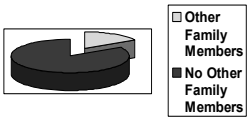
	Percent
Normal history	21.1
Normal pregnancy	24.0
Premature birth	42.9
Hyperbilirubinemia	45.7
Exchange transfusion	18.3
Anoxia	15.4
Respiratory distress	12.6
Artificial ventilation	19.4
Ototoxic drugs	27.4
Low birth weight	5.7
Anemia	4.0

*** Some infants with AN/AD have no risk factors and come through the well-baby nursery. NOT ALL infants with AN/AD are found in the NICU.*

From Berlin, Hood et al., 2008

Genetics and AN/AD

- Recessive, dominant, and mitochondrial inheritance patterns are associated with AN/AD.
- AN/AD can be part of a syndrome or non-syndromic.
- 36/225 patients comprising 16 families with AN/AD
  - *13 sibling pairs (6 pairs nonsyndromic)*
  - *3 families show a dominant pattern with multi-generational AN/AD*

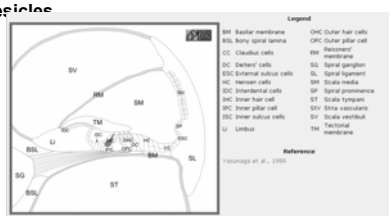


Genetics and AN/AD

- Non-syndromic recessive AN is associated with abnormalities in *OTOF – otoferlin* (Varga et al., 2003).
  - *Otoferlin* is expressed in the inner hair cells, possible roles in membrane trafficking and/or IHC synaptic vesicle fusion
  - In mice, *otoferlin* has been localized to IHC associated synaptic vesicles

OTOF expression

From: Hereditary Hearing Loss Homepage
(Smith and Van de Camp)



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

What is the incidence 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:*
- *Berlin et al., 2000* – Of 1000+ children screened in schools for the Deaf, 10-12% had either robust OAEs or evidence of residual OHC function.
- *Lee et al., 2001* - Of 72 students at schools for hearing-impaired, approximately 10% had either robust OAEs or evidence of OHC responses.
- *Rance et al., 1999* – 1 in 9 infants with permanent hearing loss had cochlear microphonics but no ABR.
- *Sininger, 2002* – Approximately 10% of infants had OAEs and no ABR in the NIDCD Newborn Screening Study.

AN/AD versus [C]APD

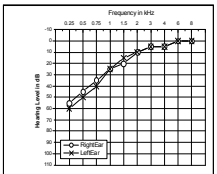
- AN/AD:
  - Synchrony disorder, possible pre-neural site
  - ABR, MEMR absent
  - Cochlear implants a management option
- Central APD
  - More diffuse in nature, peripheral synchrony usually WNL
  - ABR, MEMR usually normal
  - Cochlear implants not useful

AN/AD: Another Challenge

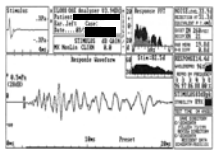
Some children are identified with AN/AD but develop speech and language without intervention, despite no recordable ABRs.

***How they come to us*:**

- **AN/AD identified at birth**
- **Often with recommendation for a cochlear implant**
- **Responsive to auditory stimuli without visual cues and speech and language is developing, on or near target**

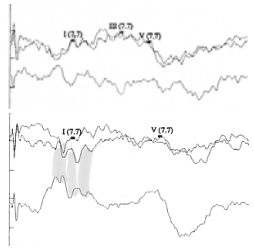


Discrim Q: 88, 92%
Discrim N: 36, 56%



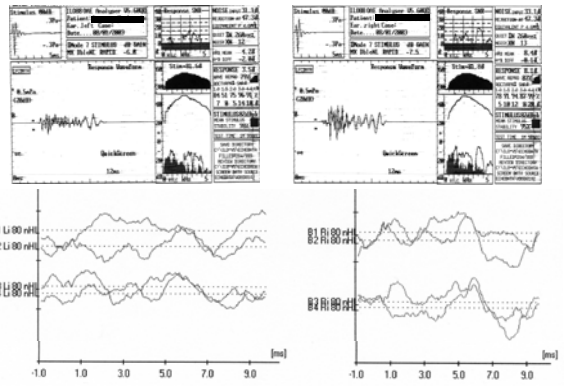
D

AN/AD patient with good recognition in quiet but poor in noise

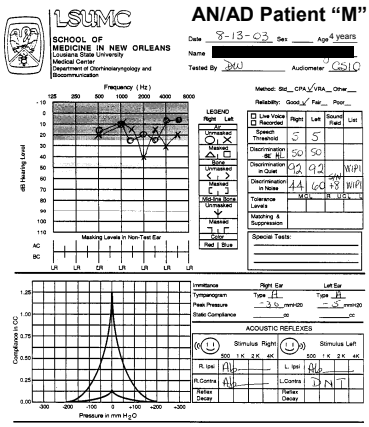


Ipsi and contra MEMRs absent

AN/AD Patient "M"



AN/AD Patient "M"



Implications for management

- **Hearing aids? Some have tried, variable benefit**
- **FM system? As their world expands, if they have difficulty in noise**
- **Cochlear implant? Monitoring speech and language development, progress in learning**
- **Communication mode? Include visual information, encourage visual contact**
- **Will they stay on track as listening situations become more challenging?**
  - ***Closely monitor; keep options open***
- **Do we have sufficiently sensitive measures to identify problems in these children?**

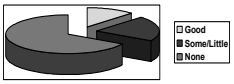
How identify these children?

- **Need objective approaches in this population**
- **Temporal processing and speech perception (e.g., Rance, 2007)**
  - **An objective measure of temporal processing ability?**
- **Cortical responses**
  - **Understanding auditory processing and effects of treatment**
  - **Some associations with speech recognition reported in AN/AD patients, though not consistent across studies**
  - **Novel stimuli and paradigms may add information**
- **Brainstem responses to speech and other novel (non-click) stimuli (e.g., BioMap – Kraus et al.)**
  - **ABR and FFR (Freq Following Resp) components of speech**

Issues in AN/AD Management: Variation in Auditory Function

AN/AD Database: Hearing Aid Use

- **Benefit from hearing aids is variable.**
  - **Limited benefit in majority of patients**
  - **Important to distinguish detection from discrimination**
  - **Optional component when evaluating cochlear implant candidacy in some practices**
- **AN/AD patients, particularly with some speech recognition ability, report benefit from FM system use when listening in background noise.**



Auditory Neuropathy/Dys-synchrony and Cochlear Implants

- **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)

Cochlear implant use

Patients with Cochlear Implants by age group

Age Group	Number
0-24 months	11
25-48 months	14
4-6 years	12
7-12 years	14
13-18 years	1
19-30 years	1
Over 30 years	1
Total	54

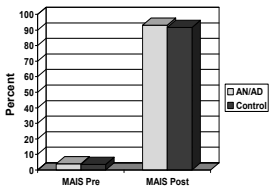
From Berlin, Hood et al., 2008

Cochlear Implant Performance

Outcomes of cochlear implantation in children with auditory neuropathy.
Peterson A, Shallop J, Driscoll C, Breneman A, Babb J, Stoeckel R, Fabry L.
J Amer Acad Audiol. 2003; 14:188-201.

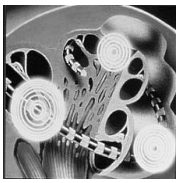
- **Matched 10 AN/AD and 10 non-AN/AD children with cochlear implants**
- **Threshold and comfort levels comparable**
- **MAIS (Meaningful Auditory Integration Scale) results comparable**

MAIS Results



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.**

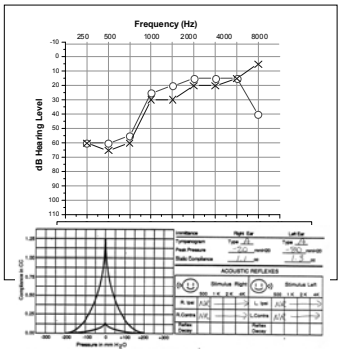


Cochlear Corporation

Patient

- Female, age: 15 years
- Increased listening difficulty, particularly with background noise
- Greater difficulty in school, losing interest
- Vision problems, progressively worsening
  - *Optic nerve atrophy*
- Other affected family members in each generation
  - *Autosomal dominant inheritance pattern*

Audiometric Results
(Age 15 years)



SRT: 20 dB R / 25 dB L

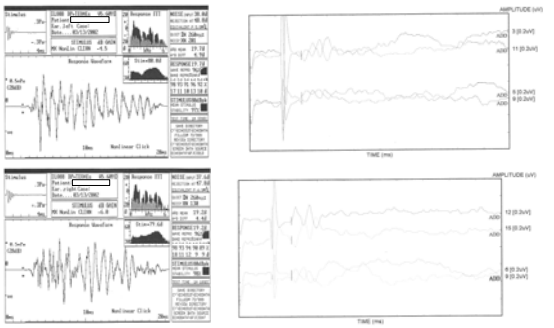
WR Quiet (40 SL):
W22*: 8% R / 10% L
CID Sentences*:
19% R / 36% L

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*

OAE and ABR Results
(Age 15 years)



Speech Recognition Results with a Cochlear Implant
(Age 16 years)

- HINT at 60 dB HL
  - 96% in quiet
  - 94% in noise at +15 S/N
- CID Everyday Sentences at 60 dB HL
  - 74% in noise at +10 S/N
  - Pre-implant reference: 0% at +10 S/N

Communication Methods

- Language Development is critical.
  - Work closely with speech/language pathologists, early interventionists, educators
- Visual Communication methods (Cued speech, sign language, signed English) are important to facilitate language development.
- Auditory Verbal Therapy by itself, before cochlear implantation, has not worked in our practice as the sole method of teaching language.

Management: Other Methods

- Preferential seating
- Note-taking service for high school and college students
- Real-time closed-captioning

Time Courses for Auditory Neuropathy

- **Stays the same**
  - **OAEs and CM remain but do not develop speech and language by auditory means alone**
    - **Some patients maintain cochlear microphonics and OAEs, but do not learn speech and language by auditory means alone.**
    - **Visual information (e.g., Cued speech, ASL, signed English) is necessary for language learning.**
    - **A number of patients in this group are successful cochlear implant users and have moved away from visual cues post-implant.**

Time Courses for Auditory Neuropathy

- **Progressive Loss of Peripheral Auditory Integrity**
  - **Loss of OAEs, CM over time**
    - **Some patients show a retrograde loss of cochlear microphonics and OAEs, and become audiologically almost indistinguishable from peripherally deaf children.**
    - **Such children have been successfully implanted and perform well with a cochlear implant.**

Time Courses for Auditory Neuropathy

- **Progressive and other neuropathies**
  - **Progressive auditory problems; develop other peripheral neuropathies (e.g., HMSN)**
    - **Some patients show a worsening of symptoms and develop other peripheral neuropathies, such as hereditary motor-sensory neuropathy (e.g., Charcot-Marie-Tooth disease).**

Time Courses for Auditory Neuropathy

- **Partial improvement**
  - **Recover some awareness of sound; continue to show desynchronized ABRs**
    - **Some patients seem to recover pure-tone sensitivity and awareness of sound, but continue to show desynchronized ABRs, robust cochlear microphonics, and normal OAEs.**
    - **Speech and language are delayed, but develop.**

AN/AD: Summary

- **Effect, directly or indirectly, is on neural processing of auditory stimuli**
  - ***Physiologic measures are needed to accurately identify AN/AD***
- **Sound processing, among other characteristics, is highly variable in patients with AN/AD**
  - **Relationships between hearing sensitivity and ability to process speech do not follow the typical hearing loss rules.**
  - **Progression, fluctuation, stability**
- **"Milder" forms of AN/AD are seen in patients of all ages**
  - **Infants/children, young adults**
  - **Older adults – a form of neural presbycusis? (e.g., Gates et al.)**

AN/AD: Summary

- **Management should proceed with thorough assessment of individual capabilities**
  - **Visual information is important in the majority of patients with AN/AD.**
  - **Cochlear implants provide significant benefit.**
  - **Distinguish detection (sensitivity) from discrimination (especially in noise) when evaluating hearing aid benefit.**
- **Follow patients closely and consider the possibility of change in auditory function over time.**

Resources

- **Listserve for parents and professionals interested in AN/AD**
  AuditoryNeuropathy@yahoogroups.com
- **My email: linda.j.hood@vanderbilt.edu**
- **Phone: 615-936-4612 (Vanderbilt University)**
- **Fax: 615-936-6914 (Vanderbilt University)**

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

Charles I. Berlin, PhD
Jill Bordelon, MCD
Leah Goforth, MS
Jennifer Jeanfreau, MCD
Li Li, MD
Thierry Morlet, PhD
Patti St. John, MCD
Melanie Thibodeaux, MCD
Diane Wilensky, MS
Harriet Berlin, MS
Shanda Brashears Morlet, MCD
Annette Hurley, PhD
Bronya Keats, PhD
Elizabeth Montgomery, MS
Kelly Rose, MA
Sonya Tedesco, MCD
Han Wen, MSBE

The Hood Lab at Vanderbilt: Heather McCaslin, AuD, Andrea Hillock, AuD, Erin Maloff, MS, Christopher Spankovich, AuD

Colleagues at Vanderbilt Bill Wilkerson Center: Gary Jacobson, PhD, Melanie Schuele, PhD, Anne Marie Tharpe, PhD, Alexandra Key, PhD., Tamala Bradham, PhD

Research supported by the NIH-NIDCD, Oberkotter Foundation, Deafness Research Foundation, American Hearing Research Foundation, National Organization for Hearing Research, Marriott Foundation, Kam's Fund for Hearing Research, Vanderbilt Development Funds