

## Diagnosis of auditory neuropathy spectrum disorder

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## Current Research Interests

- Using the speech intelligibility index (SII) to predict pediatric speech perception.
- Auditory-neuropathy spectrum disorder
- Pediatric amplification
  - Frequency lowering
  - Digital noise reduction
- Outcomes for Children with Hearing Loss (OCHL)
- Loudness perception



## Overview

- 10:30 - 12:00 Diagnosis of auditory neuropathy spectrum disorder
- 1:00 - 3:30 Step-wise management of auditory neuropathy spectrum disorder



## Diagnosis

- What is auditory neuropathy spectrum disorder (ANSD)?
  - What is **not** ANSD?
- Background information
- Diagnostic test protocol for ANSD
- Myths about ANSD diagnosis
- Illustrative case studies



## How many of you have...

- Diagnosed a child with ANSD?
- Diagnosed an adult with ANSD?
- Have **never** seen a patient with ANSD?
- Don't know if you have seen a patient with ANSD?



### What is ANSD?

- Broad definition
  - Abnormal auditory nerve function
    - Absent or significantly abnormal ABR
    - Absent acoustic reflexes
  - AND
    - Normal cochlear outer hair cells (OHC)
      - Present otoacoustic emissions (OAEs)
      - Cochlear microphonic on ABR



### A brief historical digression....

- ANSD is not new
- What is new?
  - Ability to document outer hair cell function
    - OAEs
    - Cochlear microphonic
  - Universal newborn hearing screening
  - Improved NICU care
  - Integration of audiology in medicine



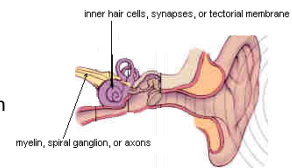
### Neuropathy? Dys-synchrony?

- Auditory neuropathy
  - Only 30% - 40% of reported cases have additional neural abnormalities
- Berlin (2001) proposed name change to auditory dys-synchrony
- Auditory Neuropathy Type I or Type II (Marsh, 2002)
- Auditory neuropathy spectrum disorder (International NHS Conference/Teagle et al. 2010; Berlin et al. 2010)



### Should we call it neuropathy?

- Neuropathy comes from neurology (“nerve damage”)
- Not all patients with ANSD have auditory nerve involvement (Rapin & Gravel, 2006)
- Current tests do not differentiate
  - MRI? Walton et al. 2008; Valero et al. 2011



### What’s the right answer ?

- Current broad definition puts a heterogeneous group of patients into one category.
- Current definition arises out of lack of specificity in available auditory tests. (SG vs. synapse vs. inner hair cell)





### A solution?

- Auditory Neuropathy Spectrum Disorder
  - Reflects the heterogeneity of individuals with the same clinical findings
  - Recognizes:
    - Variability
    - Value of diagnostic profile
    - Limitations of current tests



## How common is ANSD?

- Factors that influence prevalence estimates
  - Age
  - Population
    - NICU
    - Risk factors
    - Hearing impaired?
  - Diagnostic criteria
    - OAEs or CM?
  - Sample size

## Data from Rance, 2005


ANSD is rare, even in infants who are "at-risk"

Study	Population	No. of Subjects	No. of AN/AD Infants	% of Total
Stein et al. (1996)	Special care nursery	100	4	4.00
Pharissakis et al. (1997)	Intensive care unit	102	2	1.96
Rance et al. (1999)	"At-risk" infants	5199	12	0.23

ANSD is a small sub-group of children with permanent hearing loss



Study	Population	No. of Cases Permanent Hearing Loss	No. of AN/AD Cases	% of Total
Kraus et al. (1984)	Hg. impaired children	48	7	14.58
Park Lee (1998)	Hg. impaired children	139	7	5.04
Yahr et al. (1998)	Universal screening	111	2	1.80
Rance et al. (1999)	"At-risk" infants	109	12	11.01
Buckle et al. (2000)	Hg. impaired children	1000	87	8.70
Cox-Watson et al. (2000)	Universal screening	56	3	5.36
Lee et al. (2001)	Hg. impaired children	67	2	2.99
Madden et al. (2002)	Hg. impaired children	428	22	5.14
Tang et al. (2004)	Hg. impaired children	56	1	1.79

Small samples can lead to conclusions that ANSD is common





## Prevalence

- Foerst et al. 2006
  - n = 5190
  - 0.94% (At-risk)
  - 8.4% (Profound)
- ANSD is rare
  - 3 in 1000 children born with hearing loss
  - 1-5% children with hearing loss
  - 1-2 per 10,000 live births (estimate)


## If ANSD is rare...

- How concerned should we be?
  - Newborn hearing screening?
    - JCIH?
    - Berg et al. 2011 – Not for well-babies.
    - Amatuzzi et al. 2011 – Yes for NICU
  - Diagnostic protocols?


## Do we know the *real* prevalence?

- Audiogram is not specific
- Without an ABR, ANSD may not be detected
  - Passed OAE screening
  - Did not receive newborn hearing screening
  - Received OAE-only re-screening
- Onset may be delayed
- May be sub-group of people with undiagnosed ANSD
  - Diagnosed with SNHL
  - Misdiagnosed as having normal hearing



## What causes ANSD?

- A better question might be:
  - What *doesn't* cause ANSD?
- Diagnostic tests do not differentiate site of lesion
  - ANSD is likely multiple auditory disorders grouped under a single diagnostic category
- Multiple disorders = numerous potential causes



## Etiology of ANSD



- Risk factors may differ
  - Children
  - Adults
- Guides clinical assessment process
- *No* risk factors in some cases
  - 27% (Sininger & Oba, 2001)
  - 15% (Foerst et al. 2006)
  - 15% (Rance et al. 1999)



## Risk factors for Infants and Children

- Hyperbilirubinemia
- Hypoxia/anoxia
- Prematurity – (Amatuzzi et al. 2011 JARO)
- Infectious disease
- Genetic
  - Syndromic
  - Nonsyndromic



More than 50% of pediatric ANSD cases have one of these two factors in the birth history (Rance, 2005)



## Hyperbilirubinemia/Kernicterus

- Extent of effects may depend on:
  - Levels
  - Duration of high bilirubin levels
  - Gestational age /prematurity
  - Concurrent infection
  - Medications
  - Genetic susceptibility
- Shapiro (2010) suggests  $\geq 20$  mg/dl TSB as possible criterion for further assessment.
- Cases of AN exist in patients with  $< 20$  mg/dl.



## Hyperbilirubinemia/Kernicterus

- Improvement over time?
  - Madden et al. 2002 – 50% (n = 22) showed improvement (not recovery) over time
  - Stable by 12 – 18 months of age
  - Improvement vs. complete recovery
- Implications for cochlear implantation
- Counselling families / caregivers
- Importance of continued assessment



## Anoxia / Hypoxia

- Oxygen deprivation
- Mild Hypoxia / Mouse model – (Harrison, 1998)
  - Led specifically to IHC damage
- More severe hypoxia/anoxia may lead to brain damage / cerebral palsy in humans



## Non-Genetic Causes of ANSD

- **Systemic/Metabolic**
  - Bilirubinemia/ Kernicterus
  - Diabetes mellitus
  - Uremia
  - Alcoholism/nutritional
  - Paraproteinemias
  - Anoxia
- **Infection/Inflammatory**
  - Leprosy
  - AIDS
  - Lyme Boreliosis
- Sarcoidosis
- Polyarthritis nodosa
- Rheumatoid Arthritis
- Ramsey Hunt syndrome
- Gullain-Barre Syndrome
- **Toxins**
  - Drugs (cisplatin)
  - Heavy metals
  - Vascular diseases
  - Neoplasia
  - Trauma



### Genetic ANSD

- Syndromic w/ peripheral neuropathy
  - Charcot-Marie-Tooth
  - Mohr-Tranebjaerg syndrome
  - Friedreich Ataxia
  - > 20 other types
  - Poorer outcomes
    - Hearing aids?
    - Cochlear implants?
- Non-syndromic
  - Otoferlin mutation



### Genetic ANSD

- Age of onset may vary
  - Hereditary may not be congenital
- Rare genetic conditions may lack evidence base
- Medical genetics evaluation is for children with hearing loss
  - Identification of related medical conditions
  - Exploring etiologies associated with progressive hearing loss



### Genetic Causes of ANSD

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>•Adrenoleukodystrophy</li> <li>•Amyloid polyneuropathy</li> <li>•Charcot-Marie-Tooth 1A,1B,2,2a,2B,4A,4B,2D,X</li> <li>•Complex I, subunit ND4</li> <li>•Dejerine-Sottas syndrome</li> <li>•Friedreich's Ataxia</li> <li>•H Sensory Neuropathy type 1</li> <li>•Hereditary myelinopathy</li> <li>•HMSN (Lom)</li> <li>•HMSN and deafness</li> <li>•HNPP</li> <li>•Infantile-onset spincerebel. ataxia</li> </ul> | <ul style="list-style-type: none"> <li>•Leber optic atrophy</li> <li>•Moebius syndrome</li> <li>•Mohr-Tranebjaerg syndrome</li> <li>•Myopathy, Distal 2C</li> <li>•Neuraminidase deficiency</li> <li>•Neurofibromatosis type 2</li> <li>•NMSN, type II, with deafness</li> <li>•Phosphoribosyl PPI synthase I</li> <li>•Refsum disease (HSMN IV)</li> <li>•Refsum disease, infantile form</li> <li>•Spastic paraplegia 8</li> <li>•tRNA, mitochondrial, lysine</li> <li>•Wolfram syndrome</li> </ul> |
|---|--|



### Otoferlinopathy (DFNB9)

- Non-syndromic
  - 2% of recessive HL, 1% of all HL
- Otoferlin (OTOF)
  - Involved in synaptic vesicles of IHCs (Varga et al. 2003)
- No reported benefit from HA (Degree?)
- Successful outcome with CI (Rodriguez-Ballesteros et.al., 2003; Rouillon, 2006)
  - 10 patients implanted
  - 37 patients “phenotypically homogeneous”



### Genetics and ANSD

- Bottom line
  - Multiple genetic causes of ANSD
    - Syndromic
    - Nonsyndromic
  - Children with a family history of hearing loss
    - Need an ABR
  - Medical genetics evaluation for children with hearing loss



### Etiology of AN

- Multiple possible sites of lesion
- Numerous etiological factors:
  - Infectious
  - Teratogenic
  - Genetic
  - Traumatic
  - Interactions may exist
- Variance in etiology may explain range of auditory skills




### Age of Onset

- Infant / Young Children
  - Auditory deprivation / limited experience
  - 75% of cases
  - 25-30% have additional neurological symptoms
- Adolescent/Adult
  - Experienced auditory development
  - 25% of cases
  - 70-80% additional neurological symptoms



Intervention:

- Prognosis of associated condition
- Neural degeneration?
- Research from adults may not apply to children





### Diagnosis of ANSD

- Newborn hearing screening
- Diagnostic protocol
- Pitfalls and myths

### Newborn Hearing Screening (NHS)

- Important factors
  - Type of test
  - Protocol
  - Order of tests
- Know the tests that your local birthing hospitals use

### Age of onset


- What does this mean for newborn hearing screening?
- How should this influence our protocols for screening beyond birth?

Estimated age at onset <sup>a</sup>	Genetic defects			
	Congenital CMV (n = 10)	GSB2 mutation (n = 16)	Others <sup>b</sup> (n = 5)	Unknown (n = 36)
<2 years	10	15	5	25
Birth	2	7	2	5
<6 months	3	1	0	7
6-12 months	2	2	3	3
12-24 months	3	2	0	2
Not clear <sup>c</sup>	0	3	0	8
After 2 years	0	1	0	11

NOTE: CMV, cytomegalovirus.  
<sup>a</sup> Based on medical records and interviews with family members  
<sup>b</sup> Mendelian malformation (n = 2), Down syndrome (n = 2), or chromosomal abnormalities (n = 1)

Total number for age of onset of hearing loss  
 14 = Birth  
 28 = Post natal – 2 years  
 12 = After 2 years


From Ogawa et al. 2007




### NHS – OAE only or OAE first



- Programs screen with OAE only (cost)
- Will miss ANSD
- ABR/OAE for all infants?
  - Increased cost
  - Justified by prevalence of .014% of live births?



### Newborn Screening Protocol




OAEs

Refer Result

↓

ABR



### Implications – OAE only or first

- ANSD will be late-ID in babies who do not receive an ABR
- “Pass” on OAE hearing screening does not rule-out ANSD



### Newborn Screening Protocol



ABR



Diagnostic Evaluation



### ABR-first?

- Berg et al. 2011
  - n = > 20,000 well-babies
  - Diagnostic testing on babies that
    - Fail ABR / Pass OAE
  - < 1% of well-babies had this pattern during birth admission
  - None had this pattern at diagnostic follow-up
  - Conclusions?



### Newborn Screening Protocol



OAEs/  
Stapedial  
Reflexes

Refer Result on  
Either



ABR

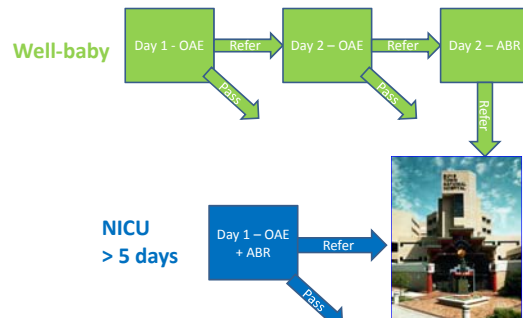



### Bergan Mercy Hospital - Omaha

- BTNRH audiologists provide newborn hearing screening
- Program staffed 365 days/year




### Bergan Protocol







## NHS - Summary

- OAE-first (if ABR is contingent on OAE) or OAE-only
  - No child with ANSD will be referred
- ABR-only or OAE + ABR
  - Children with ANSD referred
- Important to know the type of screening being done in local area
- Follow-up should be comprehensive / based on type of NHS test (ABR vs. OAE)



## NHS – Summary Continued

- Test as close to discharge as possible
- JCIH
  - ABR for children that spend > 5 days in the NICU
- Educate physicians and nurse practitioners





## Auditory Neuropathy Spectrum Disorder (ANSD)

- Broad definition
  - Abnormal auditory nerve function
    - Absent or significantly abnormal ABR
    - Absent acoustic reflexes
  - AND
  - Normal cochlear outer hair cells (OHC)
    - Present otoacoustic emissions (OAEs)
    - Cochlear microphonic on ABR


One test for auditory nerve function (at least)

One test for OHC function (at least)





## Overview- Diagnostic Test Battery

- Tympanometry
  - Evaluate middle ear function
- Acoustic Reflexes (MEMR)
  - Absent or elevated pattern
- OAEs
  - Present in many cases
- ABR
  - Present cochlear microphonic
  - Absent / abnormal neural response
- Behavioral Audiometry
  - Variable from normal to no response to pure tones
  - Speech perception difficulties in quiet and/or noise






## Tympanometry

- ANSD
  - May have normal or abnormal tympanometry
  - Presence of middle ear fluid or negative pressure or TM perforation will influence:
    - OAE / Cochlear microphonic (CM)
    - Ability to measure acoustic reflexes
- 226 Hz
  - (+ 1000 Hz probe tone < 9 months)

## Acoustic Reflexes

- ANSD
  - Absent
  - Elevated
- Berlin et al. (2005)
  - None had normal AR pattern

### Berlin et al. 2005

None of the subjects with ANSD had reflexes at both 1000 and 2000 Hz

What does suggest about a clinical protocol?

Table 1. Summary of OAE Thresholds (dB SPL) for Subjects with Present Middle Ear Muscle Responses (n = 10)

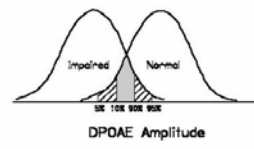
Subject	Age	Sex	Ear	Stimulus	Frequency	Level	Response
101	10	M	R	1000	1000	20	A
101	10	M	L	1000	1000	20	A
101	10	M	R	2000	2000	20	A
101	10	M	L	2000	2000	20	A
102	10	F	R	1000	1000	20	A
102	10	F	L	1000	1000	20	A
102	10	F	R	2000	2000	20	A
102	10	F	L	2000	2000	20	A
103	10	M	R	1000	1000	20	A
103	10	M	L	1000	1000	20	A
103	10	M	R	2000	2000	20	A
103	10	M	L	2000	2000	20	A
104	10	F	R	1000	1000	20	A
104	10	F	L	1000	1000	20	A
104	10	F	R	2000	2000	20	A
104	10	F	L	2000	2000	20	A
105	10	M	R	1000	1000	20	A
105	10	M	L	1000	1000	20	A
105	10	M	R	2000	2000	20	A
105	10	M	L	2000	2000	20	A
106	10	F	R	1000	1000	20	A
106	10	F	L	1000	1000	20	A
106	10	F	R	2000	2000	20	A
106	10	F	L	2000	2000	20	A
107	10	M	R	1000	1000	20	A
107	10	M	L	1000	1000	20	A
107	10	M	R	2000	2000	20	A
107	10	M	L	2000	2000	20	A
108	10	F	R	1000	1000	20	A
108	10	F	L	1000	1000	20	A
108	10	F	R	2000	2000	20	A
108	10	F	L	2000	2000	20	A
109	10	M	R	1000	1000	20	A
109	10	M	L	1000	1000	20	A
109	10	M	R	2000	2000	20	A
109	10	M	L	2000	2000	20	A
110	10	F	R	1000	1000	20	A
110	10	F	L	1000	1000	20	A
110	10	F	R	2000	2000	20	A
110	10	F	L	2000	2000	20	A

### Otoacoustic Emissions (OAE)

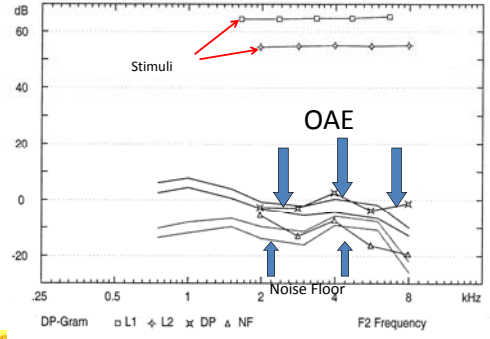
- Acoustic response from outer hair cells (OHC)
- Present in patients with ANSD
- Type not critical
  - Distortion Product (DPOAE)
  - Transient (TEOAE)

### OAEs

- Conventional wisdom
  - Normal hearing – OAEs are present
  - Hearing loss – OAEs are absent
- Distribution of OAE responses overlaps
  - NH can be absent
  - HL can be present



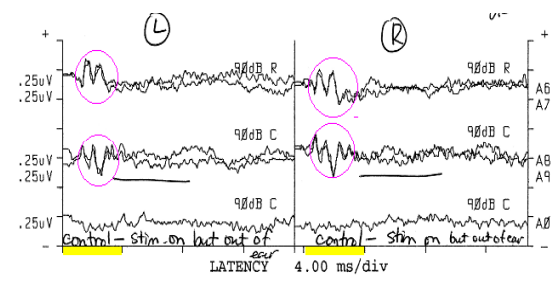
### Example – DPOAE Results



### Cochlear Microphonic

- ANSD – Present CM with absent/abnormal ABR
- Electrical OHC response
- Best recorded from EAC or location more proximal to cochlea
- May be reduced by middle ear fluid
- Reverses polarity with changes in stimulus polarity (rare / con )

### Example – Cochlear Microphonic (CM)



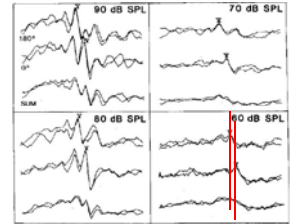
### Enhancing CM

- Measured with clicks or tone bursts
- Reduce stimulus rate (7.1/sec)
- ECoG montage
  - ECoG protocol (rare vs. con)
  - Avoid alternating polarity (unless separate recording buffers)
- Use control trials to differentiate stimulus artifact from CM



### An aside about alternating polarity

- I was taught to use alternating polarity to record ABRs
  - Reduces stimulus artifact
- Alternating polarity:
  - Lead to smearing
  - CM will not be visible
  - Stimulus artifact is rarely an issue



### Differentiating CM from Artifact

- Record for both rarefaction and condensation
- Clamp or remove sound tube
- Do not reposition transducer
  - If response persists without acoustic stimulation to the ear = stimulus artifact
  - If response disappears = CM



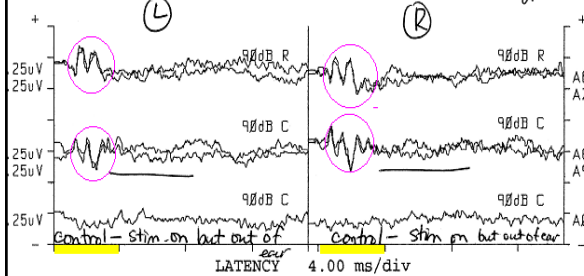
### Differentiating CM from Artifact

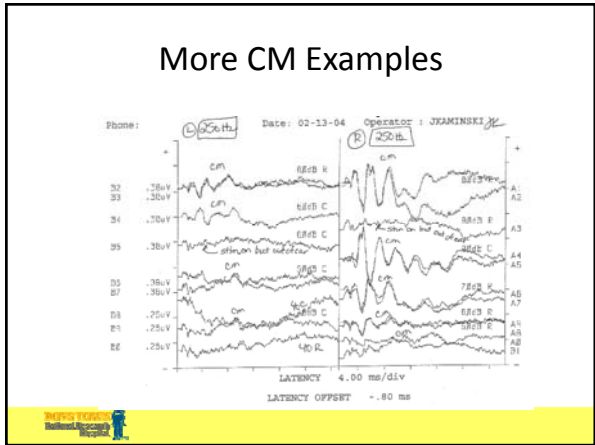
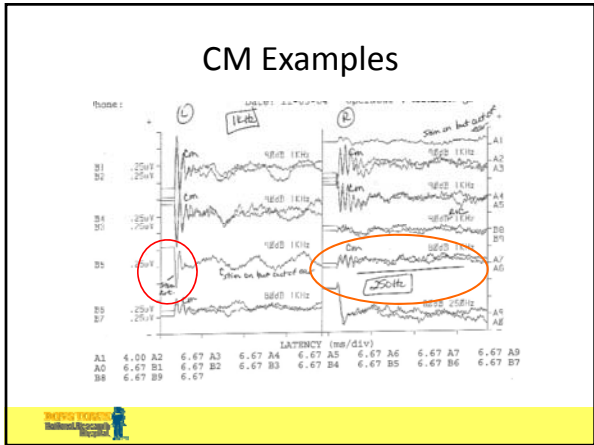
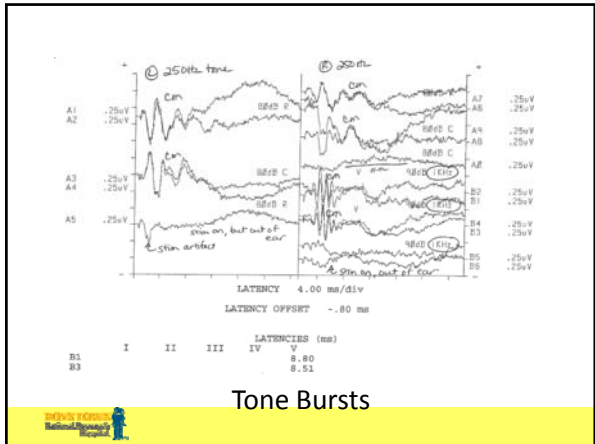
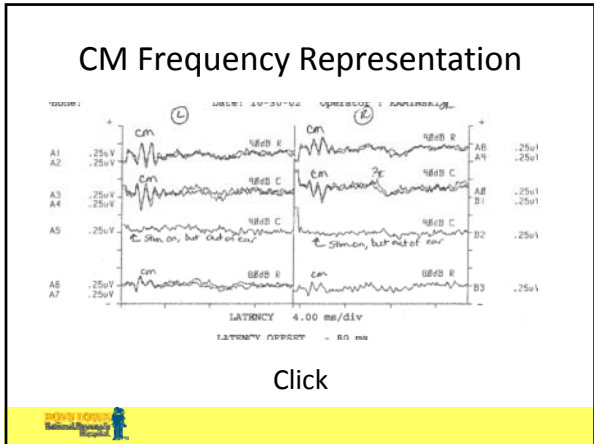


### Differentiating CM from Artifact



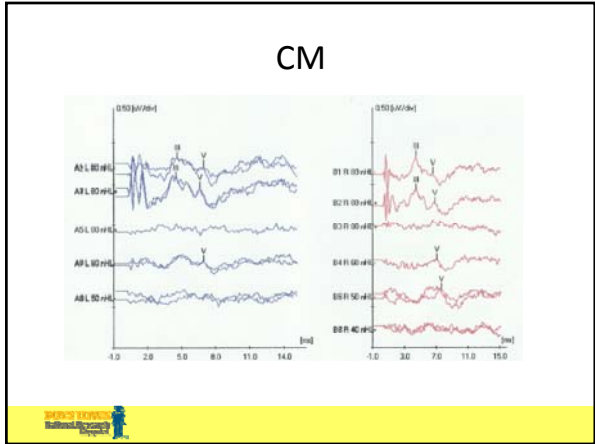
### Control Trial for CM



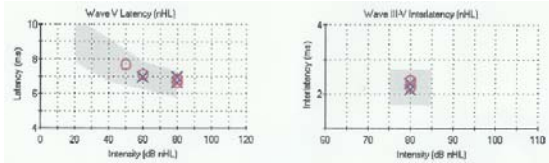


### MYTH! or FACT!

- The presence of cochlear microphonic means the patient has ANSD!



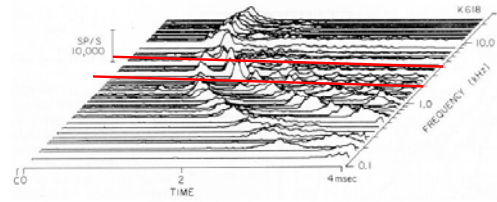
### Auditory Neuropathy ?



Normal Wave V latency  
 Absent DPOAEs  
 Despite history of kernicterus  
 What is causing us to measure CM in this patient?



### Kiang, 1975



### MYTH! or FACT!

- Both cochlear microphonic and OAEs are needed to make a diagnosis of ANSD!



### Which is more critical?

- |  |   |
|--|---|
| CM   | OAEs  |
| <ul style="list-style-type: none"> <li>•Less sensitive to ME status</li> <li>•Less frequency specific</li> <li>•Stable over time in AN</li> <li>•More difficult to record</li> </ul> | <ul style="list-style-type: none"> <li>•More sensitive to ME status</li> <li>•More frequency specific</li> <li>•Disappear over time in AN</li> <li>•Easy to record</li> </ul> |

What's the right answer?!?!?

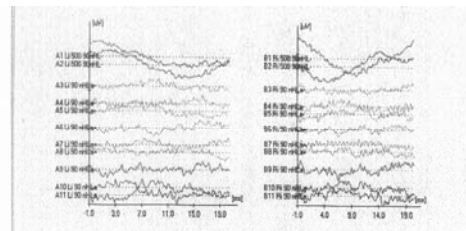


### CM and OAEs

- Diagnosis can be made by either:
  - OAEs
  - CM
  - Both (preferable)
- OAEs tend to be more "fragile"
  - Middle ear status
  - Noise
  - Decrease over time

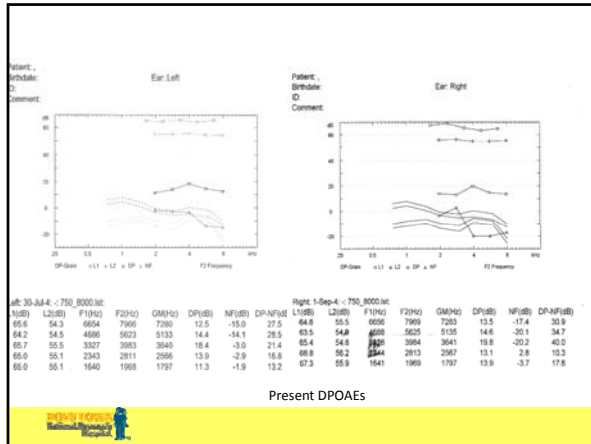


### OAEs and CM



No CM





### Auditory Brainstem Response (ABR)

- Electrical response of auditory nerve and brainstem
- Correlation with behavioral threshold is excellent (Gorga et al. 2006)
  - Normal hearing
  - Sensorineural loss

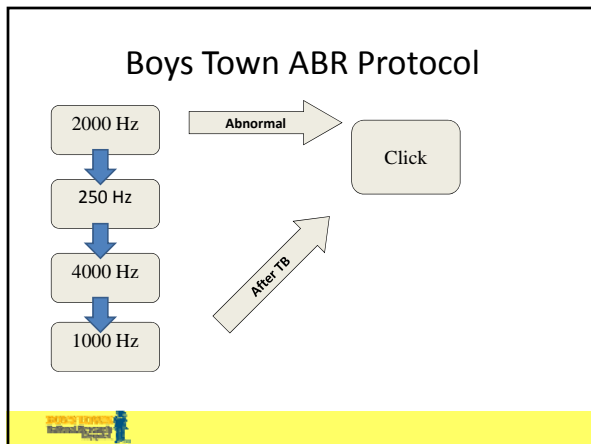
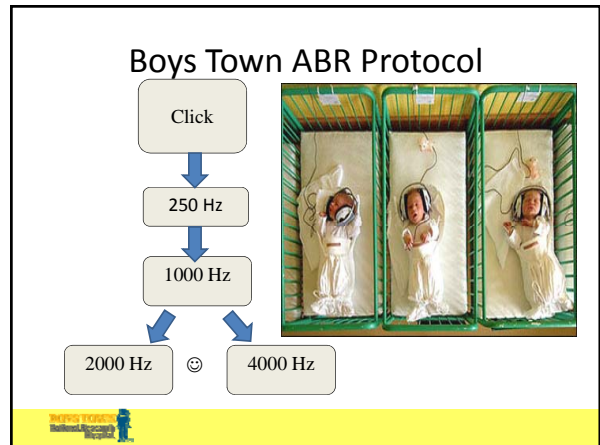
### BTNRH ABR Stimulus Parameters

- Gorga et al. 2006
  - Process
  - Test performance
    - $r = .92 - .94$
  - Clicks were good predictor of 2 - 4 kHz
- ABR Protocol
  - 2 potential approaches
  - Flexible
  - Designed to maximize data collection in short period of time

TABLE 1. Temporal characteristics and reference equivalent SPL for the five stimuli used during auditory brain stem response measurements

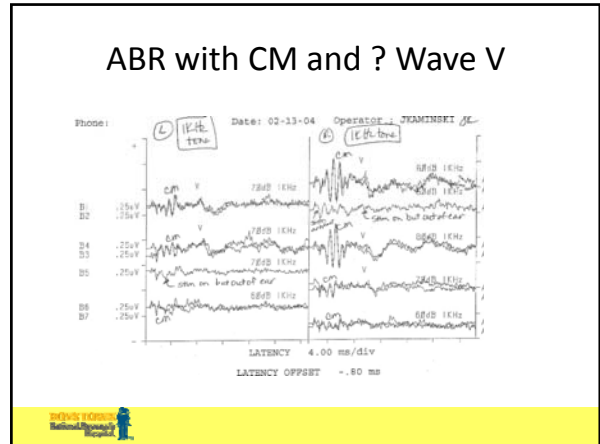
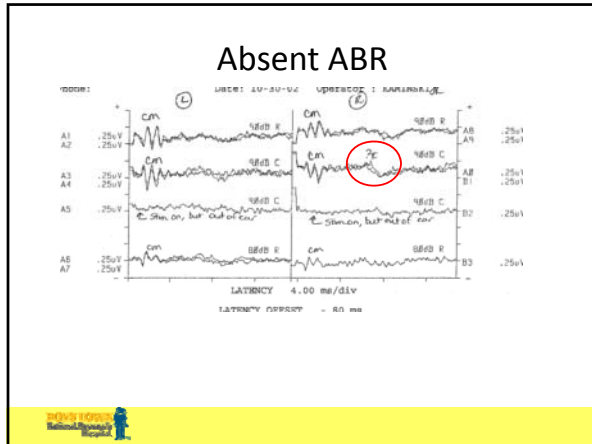
Stimulus	Rise/fall time (msec)	Plateau (msec)	Total duration (msec)	pSPL for 0 dB HL
250 Hz	2.0	0	4	43
1000 Hz	2.0	0	4	24
2000 Hz	1.5	0	3	28
4000 Hz	1.0	0	2	32
Clicks	0	0.1	0.1	35

Temporal characteristics for the click were obtained by the electrical equivalent before reproduction by the amplifier.




### ABR in ANSD

- ANSD – Absent or abnormal
  - Absent is obvious
  - What is “abnormal”?
- ABR is not a predictor of behavioral threshold



### MYTH! or FACT!

- Electrophysiological tests predict behavioral outcomes in patients with ANSD!
  - ANSD patients with a Wave V > patients without
  - ANSD patients with OAEs > patients with no OAE
  - Size of CM reflects auditory potential




### OAE, ABR, and CM

- Starr et al. 2001
  - TEOAES absent in 30% of subjects with AN
  - Abnormal ABR present in 21% (delayed Wave V)
  - CM amplitude and PTA were not different for ears with Wave V vs. those without
  - Presence/absence of TEOAES was not correlated with PTA
- Physiological tests do not predict auditory function

### Auditory Steady State Response

- ANSD – absent ASSR
  - No way to visualize CM
- Concerns about “artifact” responses
  - Gorga et al. (2004)
  - Zeng et al. (2006)
- Further research is needed



### ASSR – David Stapells

“When thresholds are elevated, ASSRs must not be used as a stand-alone electrophysiological threshold assessment...tone-evoked ABR is essential and has priority”



### SCIENCE FIGHT!

- Emara & Gabr, 2010
- Journal of Laryngology and Otology
- Auditory steady state response in ANSD
- Conclusion: The ASSR may serve as a valuable objective measure for assessing the hearing threshold .... in patients with auditory neuropathy. We recommend that ASSR be used to complete the evaluation of patients with auditory neuropathy.



### Behavioral Audiometry

- Developmentally appropriate techniques
- Provides key information about (re)habilitation
- Physiological test results do not predict audibility

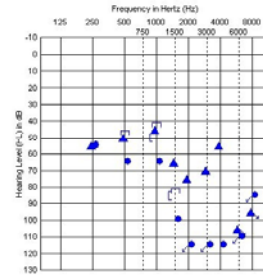


### Audiogram

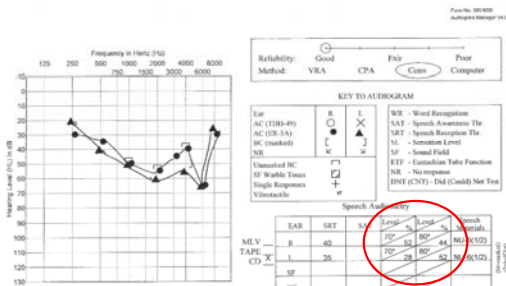
- Rising configuration
  - IHC = phase locking for low frequencies? (Heinz, et al. 2001)
- May be progressive/fluctuating
- Not an indicator of speech recognition
  - May be poorer than SNHL
  - May be the same
  - May be worse
- "Audiogram tells you nothing..."
  - Gives threshold data
  - Audibility is still critical



### Audiogram Examples



### Audiogram Examples



### Future directions in assessment

- Psychoacoustics?
  - Measures of temporal processing
- Event-related/late potentials
  - MMN & P300

