The Pathophysiology of Auditory Neuropathy Spectrum Disorders...for
Dr. Jie Wang Beijing Symposium Sept 2011
Charles I. Berlin PhD Research Professor
Otolaryngology Head and Neck Surgery
University of South Florida and Clinical
Coordinator of the All Childrens
Hospital Center for Auditory
Neuropathy Spectrum Disorders, St.
Petersburg FL
Charles.Berlin@allkids.org

All slides and teaching material will be posted online at:
• www.kresgelab.com

How different is Auditory Neuropathy/Dys-synchrony from “regular hearing loss”?
• What are the underlying physiologic differences?
• How is it diagnosed and what difference does it make...shouldn’t we still rely on the audiogram to provide guidelines for treatment and management?

A brief review of how the diagnosis of AN/AD is made?
• Absent or abnormal ABR or Electrocochleography.
• Normal, or at one time normal, otoacoustic emissions, in the presence of...
• ABSENT or Elevated Middle Ear Muscle Reflexes.
• Other signs...

To avoid missing these patients, or confusing them with CAPD patients, we recommend the following triage with each new patient as follows:
• Tympanometry
• Middle Ear Muscle Reflexes
• Otoacoustic Emissions.
• See blank Chart ...

Construct Desk Chart for Triage or sorting.

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Outer Hair Cell</th>
<th>Inner Hair cell/nerve fibers</th>
<th>Conductive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tymps/Reflex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emissions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Construct Desk Chart for Triage or sorting.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Outer Hair Cell</th>
<th>Inner Hair cell nerve fibers</th>
<th>Conductive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tymps/Reflectance</td>
<td>a</td>
<td>a</td>
<td>B and c</td>
<td></td>
</tr>
<tr>
<td>Reflexes</td>
<td>Normal levels</td>
<td>Elevated or absorbed</td>
<td>Absent or elevated</td>
<td></td>
</tr>
<tr>
<td>Emissions</td>
<td>absent</td>
<td>Present or one time present</td>
<td>Absent or reduced</td>
<td></td>
</tr>
<tr>
<td>ABR</td>
<td>Normal until threshold</td>
<td>Absent desynchronized</td>
<td>Shifted to right</td>
<td></td>
</tr>
</tbody>
</table>

**At present, how do we test outer vs. inner hair cells?**

- Outer Hair Cells can be tested with two procedures:
  - 1. Otoacoustic Emissions.
  - 2. Cochlear microphonics using insert earphones and reversing the polarity of the click at least once at the end of a completed average. (Berlin, Hood, et al. 1998)

- Inner Hair Cells can be tested with FIVE procedures:
  - EcochG
  - ABR (remember to separate CM from AP).
  - Summating Potentials.
  - Cochlear Microphonics
  - MIDDLE EAR MUSCLE REFLEXES.
  If these are absent or elevated above 95dB HL, in the presence of normal emissions, it warrants further careful investigation. (Berlin, Hood et al. 2005)

**Insert versus supra-aural earphones**

**ABR and Cochlear Microphonics**

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

- **Normal ABR to condensation and rarefaction clicks; CM inverts** -
- **AN/AD patient - all CM, no neural response**

**A Normal ABR on the Left, a Potential Trap or Misdiagnosis of Central Brain Disorder on the Right**

**Reverse the Click Polarity and What Looked Like an ABR is Revealed as a Cochlear Microphonic**
A review of the underlying physiology

- The normal human ear in motion.
- The paradox of the human threshold detection vs. the 65 dB dynamic range of the inner hair cell.
- Outer hair cell function vs. Inner Hair Cell Function (Spoendlin, Brownell, Ruggero, Jont Allen)

HOW DO THE OUTER HAIR CELLS APPEAR TO OVERCOME THIS PARADOX?

Hair Cell in Action from Jonathan Lear
Ashmore and/or Bogota Colombia Laboratory.

Displacement of the Chinchilla Basilar Membrane Relative to the Stapes
Adapted from Ruggero in Berlin, 1996

Idealized Gain Function of a Hearing Aid Which Would Do Somewhat the Same Thing in the Intensity Domain and Whose Compression Knee Begins at 40 dB Input
Adapted from Berlin, 1996

siblings with AN/AD

- Tympanometry normal
- Reflexes absent
- Emissions Present
- ABR...
- Management...
• Video of Patient before implantation.

• Video after cochlear implantation, done at the mother’s insistence...

ABR from subjects with “corner audiograms” and Otoferlin mutations affecting inner hair cells.

Temporal Bone of Premature, Amatuzzi et al. June 2001 Arch Otolaryngology
Normal nerve fiber count inside the habenula perforata.

Note missing Inner Hair cell, normal nerve fiber count inside the habenula perforata, and normal outer hair cells which would lead to normal emissions and NO ABR.

A normal ear; B selective OHC loss; C combined IHC and OHC loss; D-F complete IHC loss with scattered or no OHC loss.

Alternatively, Starr et al. show this type of pathophysiology.

Comparing a normal cochlea (right) to one with Auditory Neuropathy.
From Starr et al. MPZ Gene paper

Inner Hair Cells in Auditory Neuropathy

More from Starr paper

Auditory neuropathy

Auditory Nerve (400x)
AN Control

Auditory Nerve (1500x)

My patients are mostly adults,

Does this happen much in adults?
See Brian CJ Moore and Chris Turner and their work on Dead Zones and see for example:


Patient who acquired AN/AD

- History of normal hearing until she was beaten unconscious by an abusive boyfriend
- Claimed subsequently to be totally deaf to speech and pure tones
- Tymanometry normal
- Emissions normal
- Initially diagnosed from emissions alone as "hysterical" or "malingering"
- BUT Reflexes (done only by us) ABSENT
Movie of a patient I (CB) initially mis-diagnosed as having CAPD
• \Teaching Material and papers\Ali’s Film

AN/AD versus and central auditory processing disorders

Case Study
- 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”

Audiogram and DPOAEs: First Test

Middle Ear Measures
• Tympanograms: Normal
• Ipsilateral reflexes: Absent
• Contralateral reflexes: Absent
• Non-acoustic reflexes: Present

Speech Audiometry
• Word recognition in quiet:
  – Right ear: 84% at 40 dB SL
  – Left ear: 8% at 40 dB SL, 48% at 60 dB HL
• Word and sentence recognition in noise: 0% at signal-noise ratio of +10 dB
Radiological and neurological evaluations

- **CT Scan with contrast and MRI**: Normal
- **Neurological evaluation**
  - Dx of Charcot-Marie-Tooth syndrome
    - A group of genetically determined polyneuropathies with distal muscle weakness, atrophy and sensory nerve involvement; demyelinating
- **Management**
  - Lipreading, preferential seating, visual information, note-taking service, real-time closed captioning,

AN/AD versus CAPD

- **AN/AD**:
  - Synchrony disorder, possible pre-neural site
    - Inner hair cells, synapse, VIIIth nerve
    - ABR, MEMR absent
    - Cochlear implants beneficial
- **Central APD**:
  - More diffuse in nature
    - Peripheral neural synchrony usually normal (VIIIth n.)
    - ABR, MEMR usually normal or near normal
    - Cochlear implants not useful

Phenotyping AN/AD: Variable Characteristics and Time Courses

- **Onset**
  - Congenital, later onset, acquired
- **Progression**
  - Progressive worsening (loss of peripheral auditory integrity; component of other progressive peripheral neuropathy)
  - Stays the same
  - Partial recovery of auditory ability (improved pure tones and sound awareness despite continued dys-synchrony)
- **Genetic patterns**
  - Dominant, recessive, non-syndromic, syndromic, mitochondrial
- **Auditory sensitivity and ability to utilize speech information**

Kresge Lab AN/AD Database

- **Total confirmed patients with AN/AD = 225**
  - Based on present OAEs and/or CM and absent/abnormal ABR
- **Age**
  - 0-24 months 67
  - 25-48 months 42
  - 4-6 years 36
  - 7-12 years 38
  - 13-18 years 5
  - 19-30 years 13
  - >30 years 16
  - Unknown 8
- **46% female; 54% male**
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