Auditory Neuropathy Spectrum Disorder
Christina L. Runge PhD, CCC-A
Chief, Division of Communication Sciences
Director, Koss Cochlear Implant Program
Department of Otolaryngology and Communication Sciences
Medical College of Wisconsin, Milwaukee, WI

Acknowledgements
NIH/NIDCD K23DC008837
Genotype-Phenotype Relationships in Auditory Neuropathy
Koss Cochlear Implant Program
Department of Otolaryngology and Communication Sciences
Medical College of Wisconsin
Milwaukee, WI
Masters Family Speech and Hearing Center
Children’s Hospital of Wisconsin
Milwaukee, WI

Learning Objectives
• Define the clinical audiologic findings necessary to diagnose ANSD
• Be familiar with medical conditions requiring further evaluation due to a strong association with ANSD
• Understand assessment and intervention option for children with ANSD
Multi-Disciplinary Program

ANSD Background

Nomenclature

- Auditory neuropathy (AN)
- Auditory dys-synchrony (AD)
- Auditory neuropathy/dys-synchrony (AN/AD)
- Auditory neuropathy spectrum disorder (ANSD)
Clinical Definition

• Present outer hair cell function
  – Otoacoustic emissions (OAEs)
  – Cochlear microphonic (CM)
• Dys-synchronous neural activity
  – Absent or abnormal ABR
  – Absent or elevated middle ear reflexes

Clinical Definition

• Various audiometric configurations
• Unusually poor speech perception
  – Particularly in noise
• Temporal processing disorder

Speech Perception with ANSD

• Temporal information is important for encoding speech
  – Low to mid frequencies
• Temporal impairment and/or degraded signal (i.e., in noise) significantly impacts speech perception
Auditory Neuropathy - Severe

Diagnosis of ANSD

Newborn Hearing Screening
- Newborn Hearing Screening
  - OAE screen will miss ANSD
  - ABR screening needed for babies in the NICU or with risk factors
- Neonatal risk factors
  - Family history of ANSD
  - Anoxia
  - Hyperbilirubinemia
  - Premature birth
  - Exchange transfusion
Evoked Potentials

- OAEs and/or CM
  - Outer hair cell function
- ABR
  - Auditory nerve and brainstem function
- Middle ear reflexes
  - Auditory reflex pathway function

Otoacoustic Emissions

- Transient-Evoked (TEOAEs) or Distortion Product (DPOAEs)
- General criteria for present OAEs
  - Must be 4-6 dB above the noise floor
  - Must be reproducible
  - Must be present across multiple frequencies/octave bands
- Present in approximately 75% with ANSD

Transient-evoked OAEs
Auditory Brainstem Response

- Use ANSD protocol when ABR absent at high stimulus levels (80-90 dB HL)
- Test parameters:
  - Insert earphones
  - Click stimuli at 80-90 dB HL
  - Record ABR to both condensation (+) and rarefaction (-) stimuli
  - Record ABR to alternating polarity (+,-) stimuli
  - Record with insert earphone tube pinched

Auditory Brainstem Response

- Present cochlear microphonic
  - Initial peak latency ~0.4 ms
  - Persists for several milliseconds
  - 180° phase shift follows reversal in stimulus polarity
- ABR
  - Observed when CM is cancelled out
  - Absent or abnormal morphology
  - Pinched tube recording should show no response
Middle Ear Muscle Reflexes

• Absent if no reflex ≥ 110 dB HL
• Elevated if reflex > 95 dB HL
• Caution with interpretation in young infants
  – High frequency probe tones for MEMRs are not established in this population
• MEMRs should be confirmed with ABR using the ANSD protocol

Imaging Considerations for ANSD

• Abnormalities found in 64% with ANSD
  – 18% have absent/deficient auditory nerve
• Assess status of brain
• Assess the status of the auditory nerve
• Para-sagittal oblique reconstructions
• CN VIII > CN VII (about twice as thick)
  – at level of brainstem
Nerves of the IAC

- Facial nerve
- Cochlear nerve
- Inferior vestibular nerve
- Superior vestibular nerve

Normal MRI

Abnormal MRI
PHACE Syndrome

- Infantile hemangiomas
- Posterior fossa malformations
- Aorta and cardiac defects
- Eye abnormalities

Genetic Testing for ANSD

- Associated with ANSD: OTOF, PJVK, SLC19A2
- Associated with SNHL and peripheral neuropathy: PMP22, MPZ, FXN
- Screen for common GJB2 and GJB6
Mutations associated with ANSD

• Otoferlin (OTOF)
  – OTOF is expressed in the inner hair cells
  – Affects calcium binding and vesicle docking

Otoferlin Mutations

• DFNB 9 Phenotype
  – Profound bilateral hearing loss
• Fluctuating Hearing Phenotype
  – Temperature-sensitive
  – May be heterozygous for mutation

Temperature-Sensitive ANSD

• 14 year-old boy
• Hx of hearing fluctuation
  – Illness/fever
  – Physical exercise/exertion
  – Exposure to warm temperatures
• Otoferlin mutation
  – Allele 1: 2389 T>C
  – Allele 2: Wildtype
Temperature-Sensitive ANSD

Charcot-Marie Tooth
- Peripheral neuropathy
- Later manifestations:
  - Foot deformity (very high arch to feet)
  - Foot drop (inability to hold foot horizontal)
  - Loss of lower leg muscle, which leads to skinny calves
  - Numbness in the foot or leg
  - "Slapping" gait (feet hit the floor hard when walking)
  - Weakness of the hips, legs, or feet
- No cure

Freidereich’s Ataxia
- Most common ataxia
- Nervous system degeneration
- Manifestations between 5-15 years old:
  - Difficulty walking
  - Muscle weakness
  - Speech problems
  - Involuntary eye movements
  - Scoliosis
  - Heart palpitations
Candidate Mutation Summary

<table>
<thead>
<tr>
<th>Pheno</th>
<th>Gene/Locus</th>
<th>Mutation Codon</th>
<th>Ex/Intr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1469</td>
<td>C&gt;A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P490Q</td>
<td>Ex15</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1601</td>
<td>delC</td>
</tr>
<tr>
<td>AN/AD</td>
<td>MPZ</td>
<td>1q21.3-q23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>434</td>
<td>A&gt;C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y145S</td>
<td>Ex3</td>
</tr>
<tr>
<td>DFNB9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2239</td>
<td>G&gt;T</td>
</tr>
<tr>
<td>AN/AD</td>
<td>MPZ</td>
<td>1q21.3-q23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>371</td>
<td>C&gt;T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T124M</td>
<td>Ex3</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1651</td>
<td>delG</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2649</td>
<td>C&gt;A</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>293</td>
<td>G&gt;C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R98P</td>
<td>Ex3</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2122</td>
<td>C&gt;T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R708X</td>
<td>Ex19</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2348</td>
<td>delG</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2381</td>
<td>G&gt;A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R794H</td>
<td>Ex21</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2485</td>
<td>C&gt;T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q829X</td>
<td>Ex22</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3032</td>
<td>T&gt;C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L1011P</td>
<td>Ex26</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4275</td>
<td>G&gt;A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W1425X</td>
<td>Ex36</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4491</td>
<td>T&gt;A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y1497X</td>
<td>Ex37</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4483</td>
<td>C&gt;T</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5011</td>
<td>dupT</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5384</td>
<td>T&gt;G</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5473</td>
<td>C&gt;G</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P1825A</td>
<td>Ex44</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5860</td>
<td>C&gt;G</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P1987R</td>
<td>Ex48</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6014</td>
<td>G&gt;A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R1939Q</td>
<td>Ex48</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>709</td>
<td>C&gt;T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R237X</td>
<td>Ex8</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>724</td>
<td>delC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>del242fs/X25</td>
<td></td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>750</td>
<td>G&gt;A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W250X</td>
<td>Ex2</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>765</td>
<td>G&gt;C</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>484</td>
<td>C&gt;T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R162X</td>
<td>Ex2</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1180</td>
<td>dupG</td>
</tr>
<tr>
<td>R-B</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1236</td>
<td>delC</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>515</td>
<td>G&gt;A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G172D</td>
<td>Ex2</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>547</td>
<td>C-T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R183W</td>
<td>Ex4 -3263 T&gt;G Promoter</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>547</td>
<td>G-T</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5860</td>
<td>C&gt;G</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P1987R</td>
<td>Ex48</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>6014</td>
<td>G&gt;A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R1939Q</td>
<td>Ex48</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>709</td>
<td>C&gt;T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R237X</td>
<td>Ex8</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>724</td>
<td>delC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>del242fs/X25</td>
<td></td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>750</td>
<td>G&gt;A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>W250X</td>
<td>Ex2</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>765</td>
<td>G&gt;C</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>484</td>
<td>C&gt;T</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R162X</td>
<td>Ex2</td>
</tr>
<tr>
<td>AN/AD</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1180</td>
<td>dupG</td>
</tr>
<tr>
<td>R-B</td>
<td>OTOF</td>
<td>2p23</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1236</td>
<td>delC</td>
</tr>
</tbody>
</table>

Intervention with ANSD: Hearing Aids and Cochlear Implantation

ANSD Audiometric Profile

- Normal: 30%
- Aidable: 67%
- Profound: 3%

N=258 ears

Berlin et al., IntJAud 2010;49;30-43.
Hearing Aids
• Fit as early as possible
• Fit gain to the hearing loss
  – Ensure audibility
  – Do not try to ‘protect’ OAEs with mild-gain HAs
• Should improve sound detection
• Assess auditory skill progress
• Assess speech and language development

Auditory Skill Assessment
• Assessment intervals
  – Before HA fitting (baseline)
  – Every 3 months after HA fitting
  – At end of HA trial (if not on a 3-month interval)
• LittlEARS: milestone assessment
  – Receptive auditory behavior (sound detection)
  – Semantic auditory behavior (comprehension)
  – Expressive-vocal behavior

LittlEARS
• First 24 months of intervention
• Standardized on normal hearing children
• Track development trajectory
  – Identify plateaus
  – Intervention, therapy
Speech/Language Assessment

- Assessment intervals
  - At 6 mo of age, or upon identification if older
  - Every 6 months after
  - Therapy sessions to become familiar with child
- Follow longitudinally
  - Determine progress
  - Quantify delay (if present)

Cochlear Implant Candidacy

- Is a child with ANSD a CI candidate?
  - Profound hearing loss (30%)
  - Normal to severe loss (70%)
- Acoustic benefit
  - Progress in auditory and speech-language skills
  - Currently no strict criteria for determining implantation in ANSD

Cochlear Implantation

- Restore neural synchrony
  - EABR, ECAP present
- Outcomes often positive
  - 85% successful (Berlin et al., 2010)
- Potential contraindications to CI
  - Severe or central neuropathy (keratitis, Friedreich’s Ataxia)
  - Absent auditory nerve
**ANSD – Profound HL and CI**
- 7 year-old girl
- Cystic fibrosis
- Failed NB screen (ABR)
- Diagnostic +OAEs, -ABR
- Minimal progress with HAs
- Otoferlin homozygous (Runge et al., 2013)
- Cochlear Implant at 1.5 years
- 56% PBK words
- 90%(Q), 90% (N) HINT-C Sentences

**ANSD – Moderate HL and CI**
- 10 year-old boy
- Hyperbilirubinemia, preemie
- 2 mos: +OAEs, -ABR
- Hearing aids at 1 year
  - Improved detection only
- Cochlear implant at 3 years
- 68% PBK words
- 94%(Q), 91% (N) HINT-C Sentences

**ANSD – Moderate HL and HAs**
- 8 year-old boy
- Twin-to-twin transfusion
- 9 months +CM, -ABR
- Mild-moderate hearing loss
- Normal speech and language development
- 76% PBK words in quiet
- Difficulty in noise
Can AN ‘reverse’?

- Very rare
- High-risk infants: premature, low birth weight, hyperbilirubinemia
- Improvement emerging or complete by 7-12 months of age
- Repeat ABR testing to ensure stability
  - Always before a cochlear implant

Summary

- ANSD is a unique hearing disorder
  - Temporal impairment
  - Distinct from SNHL
- Requires special tests and close follow up
  - Evidence-based protocol
- Multi-disciplinary clinical care
  - Communication among professionals and parents
- Research