Identification, Diagnosis, and Management of Auditory Neuropathy Spectrum Disorder (ANSD)

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Definition of Auditory Neuropathy Spectrum Disorder
Mechanisms and Associated Diseases, Prevalence
Identification of ANSD
Diagnosis of ANSD
Audiologic Characteristics of ANSD
Management Strategies and Outcomes

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AUDITORY NEUROPATHY SPECTRUM DISORDER: Early literature reporting normal OAEs and abnormal ABRs (1)
- Prieve, Gorga & Neely. JSHD 34: 1991
- Baldwin & Watkin. J Laryngol & Otol 106: 1992
- Katona et al. IJPORL 26: 1993
- Stein et al. Seminars in Hearing 17: 1996

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AUDITORY NEUROPATHY SPECTRUM DISORDER: Early literature reporting normal OAEs and abnormal ABRs (1)
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AUDITORY NEUROPATHY SPECTRUM DISORDER: Early literature reporting normal OAEs and abnormal ABRs (2)

- Deltenre et al. EEG & Clin Neurophys 104: 1997
- Parker, Webb & Stevens, Brit Soc Audiology, 1997
- Psarommatis et al. IJPORL 39: 1997
- Miyamoto et al. Laryngoscope 109: 1999
- Rance et al. Ear & Hearing 20: 1999
- Almost a thousand publications

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Identification, Diagnosis, and Management of Auditory Neuropathy Spectrum Disorder (ANSD): Characteristic Pattern of Auditory Findings

- Auditory brainstem response (ABR)
  - Absent ABR with no wave I
- OAEs
  - Normal or present initially
  - 98% still have OAEs over time (Sanvelbhaa et al. IJPORL, 77, 2013)
- Cochlear microphonic (CM) OAEs
  - Present with rarefaction versus condensation stimuli
- Absent acoustic reflexes
- Pure tone audiometry
  - Variable from normal to rising pattern to no response
- Speech audiometry
  - Poor word recognition relative to hearing thresholds
  - Very poor speech perception in noise

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Identification, Diagnosis, and Management of Auditory Neuropathy Spectrum Disorder (ANSD)

- Cerebello-pontine angle (CPA)
- Internal auditory canal (auditory nerve)
- Spiral ganglion cells
- IHC - 8th cranial synapse (glutamate)
- Inner hair cells
- Outer hair cells
- Inner hair cells
- Outer hair cells
- Basal ganglion cells
- MC - 10 cranial synapse
AN pattern of auditory findings (e.g., normal OAEs with hearing loss and/or no ABR) first identified in late 1980s and early 1990s

“Auditory neuropathy” coined in 1996 by neurologist Arnold Starr

Normal outer hair cell function by OAE or ECochG and abnormal afferent auditory function (abnormal ABR)

8/10 patients with “AN” had generalized peripheral neuropathy

Post-synaptic, i.e., type II AN (Starr et al, 1996)

Pre-synaptic, i.e., type I AN (Starr et al, 1996)

Concerns about terminology

“Auditory dysynchrony” (Berlin et al, 2001)

“Auditory neuropathy” senso stricto (Rapin & Gravel, 2002, 2006)

Inaccurate reports of sensory or non-neural etiologies, e.g.,

- Inner hair cell dysfunction
- Abnormal but not absent ABR

We object on scientific grounds to the use of the term “auditory neuropathy” when the main site of pathology is in the brain stem or more centrally in the auditory pathway. Loose use of the term “auditory neuropathy” is confusing, likely to be anatomically incorrect, and engenders imprecision rather than emphasizing the strong need for comprehensive behavioral, electrophysiological, and pathologic investigation. … Therefore, we urge that the term auditory neuropathy senso stricto be reserved for demonstrable involvement of the spiral ganglion cells or their processes, and not be used for pathologies of uncertain or mixed locations (p. 724).

AUDITORY NEUROPATHY SPECTRUM DISORDER: Proper Terminology (“Senso Stricto”)

According to Isabelle Rapin and Judy Gravel (2003)

Judy Gravel (1948 - 2008)

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In June 2008, at the invitation of Deborah Hayes, a panel of experts met in Como, Italy at the NHS 2008 Conference to develop Guidelines for the Identification and Management of Infants and Young Children with Auditory Neuropathy.

The panel consisted of:

- Yvonne Sininger, Ph.D.
- Arnold Starr, M.D.
- Christine Petit, M.D., Ph.D.
- Gary Rance, Ph.D.
- Barbara Cone, Ph.D.
- Kai Uus, M.D., Ph.D.
- Patricia Roush, Au.D.
- Jon Shallop, Ph.D.
- Charles Berlin, Ph.D.
Rationale for NHS 2008 Conference decision on term "ANSD"

First, despite potentially inexact usage, the term 'auditory neuropathy' has gained widespread acceptance, both in the professional literature and among parent/consumer organizations. Renaming the disorder is not feasible.

Second, the expression of this disorder in everyday listening and communication behaviors encompasses a spectrum ranging from limited or mild effects to profound effects (functionally 'deaf').

Third, the term "spectrum" was felt to expand the concept of the disorder to include sites of lesion other than the auditory nerve.

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Identification, Diagnosis, and Management of Auditory Neuropathy Spectrum Disorder (ANSD)

- Perinatal Diseases
  - Hyperbilirubinemia
  - Hypoxic insults
  - Ischemic insults
  - Prematurity and low birth weight
- Neurological Disorders
  - Demyelinating diseases
  - Hydrocephalus
  - Immune disorders, e.g., Guillain-Barre syndrome
  - Inflammatory neuropathies
  - Severe developmental delay

Auditory Neuropathy Spectrum Disorders (ANSD): Associated Medical Diagnoses (2)

- Neuro-metabolic diseases
- Genetic and Hereditary Etiologies
  - Family history
  - Otoferlin (OTOF) gene
  - Non-syndromic recessive auditory neuropathy
  - Hereditary motor sensory neuropathies (HMSN), e.g., Charcot-Marie-Tooth syndrome
  - Leber's hereditary optic neuropathy
  - Waardenburg's syndrome
  - Neurogenerative diseases, e.g., Friedreich's ataxia
- Mitochondrial disorders, e.g., mitochondrial enzymatic defect
Medical Diagnoses in ANSD: A Sampling of Recent Literature

Hyperbilirubinemia

- Auditory impairment is linked to high bilirubin levels. Shapiro & Popelka. Seminars in Perinatology, 2011.

- Auditory neural damage from bilirubin toxicity ranges from neural timing deficits, including neural firing delays and dyssynchrony, to neural response reduction and even elimination of auditory neural responses. This condition is comprehensively described as auditory neuropathy spectrum disorder.


- Our findings strongly suggest that auditory neuropathy spectrum disorder is a common manifestation of acute bilirubin-induced neurotoxicity in late preterm and term infants with severe jaundice.

Neuro-degenerative diseases


- 'Auditory neuropathy' (AN), the term used to codify a primary degeneration of the auditory nerve, can be linked directly or indirectly to mitochondrial dysfunction. These observations are based on the expression of known mitochondrial-based neurological diseases (Friedreich's ataxia, Mohr-Tranebjærg syndrome).


- Basic auditory processing was affected with each FRDA individual showing poorer temporal processing and figure/ground discrimination than their matched control. Speech perception in the presence of background noise was also impaired, with FRDA listeners typically able to access only around 50% of the information available to their normal peers.

- The use of personal FM-listening devices did however, dramatically improve their ability to hear and communicate in everyday listening situations.
Medical Diagnoses in ANSD: A Sampling of Recent Literature

- **Neuro-degenerative diseases**
  - The aim of this study was to investigate auditory pathway function, speech perception ability and everyday listening and communication in children of school age with inherited neuropathies.
  - While each subject had normal or near-normal sound detection, individuals in both disease groups showed electrophysiological evidence of auditory neuropathy with delayed or low amplitude auditory brainstem responses.
  - Auditory perception was also affected, with >60% of subjects with Charcot-Marie-Tooth type 1 and >85% of Charcot-Marie-Tooth type 2 suffering impaired processing of auditory temporal (timing) cues and/or abnormal speech understanding in everyday listening conditions.

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Medical Diagnoses in ANSD: A Sampling of Recent Literature

- **Genetic etiologies**
  - Research on the genetic causes of isolated auditory neuropathies has been remarkably successful in the last few years.
  - This knowledge is permitting to classify isolated auditory neuropathies into etiologically homogeneous types, so providing clues for the better diagnosis, management and therapy of the affected subjects.

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Medical Diagnoses in ANSD: A Sampling of Recent Literature

- **Genetic etiologies**
  - This paper has provided an overview of mutation with some of the genes and/or loci discovered to be the cause for auditory neuropathy spectrum disorders (ANSDs).
  - These discoveries have provided us with vital information as to the sites of pathology in auditory neuropathy spectrum disorders (ANSDs), and the results highlight the heterogeneity of the disorder.
Medical Diagnoses in ANSD: A Sampling of Recent Literature

- Genetic etiologies
  - OTOF (otoferlin)
    - DFNB9 non-syndromic hearing impairment
      - Affects neurotransmitter release at base of IHCs
      - Interferes with precise coding of sound via the synapse
        between IHCs and afferent fibers
    - IHC ribbon synapse critical for faithful temporal coding
      of auditory inputs
      - Nine different mutations of OTOF were detected, and seven of them were novel.
    - May be temperature sensitive in some cases
    - These results support the clinical significance of comprehensive mutation screening for auditory neuropathy.

ANSD: Published Findings on Mechanisms

- 30 to 40% of patients with AN have evidence of other peripheral nerve disorders (e.g., Starr)
- As many as 80% of AN patients have some degree of peripheral neuropathy (e.g., Hereditary sensory motor neuropathy, Friedrich's ataxia)
- Human temporal bone studies confirm in some cases normal hair cells and ganglion cell abnormality (e.g., Nadol, Starr)
- Some children with audiology pattern consistent with AN have small or absent auditory nerve (9/51 children, or 18%, reported by Buchman, Roush, Teagle, et al. Ear & Hearing, 2006)
- Otoferlin mutations (DFNB59) affect excitatory neurotransmitter release at base of inner hair cells, accounting for 3.5% of non-syndromic hearing loss (Rodriguez-Ballesteros et al, Human Mutation, 2003)
Comprehensive Assessment of Auditory Neuropathy Spectrum Disorder (ANSD): MRI of Auditory Nerve

- Brainstem and inner ear abnormalities in children with auditory neuropathy spectrum disorder and cochlear nerve deficiency. Huang et al. (UNC). American J Radiol, 31, 2010

- CND was identified in 33.0% of children and 26.9% of ears with ANSD. Significantly more patients with bilateral CND had intracranial abnormalities than those with unilateral CND (60.0% versus 15.8%).


- Cochlear nerve deficiency can be seen by electrophysiological evidence and may be a significant cause of unilateral AN. Inclined sagittal MRI of the internal auditory canal is recommended for the diagnosis of this disorder.

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Identification of Auditory Neuropathy Spectrum Disorder: Minimal Test Battery (2008 ANSD Guidelines)

- Tests of cochlear hair cell function
  - Otoacoustic emissions (OAEs)
  - Cochlear microphonic (ECochG and ABR)
    - CM may be present with absent OAEs (e.g., middle ear disorder)

- Tests of auditory nerve function
  - ABR for high and moderate intensity click stimulation
    - Separate averages for rarefaction stimulus polarity
    - Separate averages for condensation stimulus polarity

Additional tests are supplemental

- Acoustic reflex measurement (generally absent in ANSD)
- Suppression of otoacoustic emissions (no suppression in ANSD)
Diagnosis of Auditory Neuropathy Spectrum Disorder (2008 Guidelines)

- Diagnostic audiologic assessment
- Pediatric and developmental history
  - Otologic evaluation, plus
    - Imaging of cochlea with CT
    - Imaging auditory nerve with MRI
  - Medical genetics evaluation
  - Ophthalmologic evaluation
  - Neurological evaluation to assess:
    - Peripheral nerve function
    - Cranial nerve function
- Communication assessment

Three principle reasons for comprehensive assessment
- "Defining etiology of ANSD is important for predicting:
  - Whether condition is transient or permanent
  - Determining if medical or surgical treatment is needed
  - Answering parent’s questions about cause of hearing disorder"
- Infants with ANSD (especially graduates of NICU) are at risk for additional disabilities. Early identification of developmental delays is important for optimal child development
- Infants with ANSD may develop additional cranial or peripheral neuropathies secondary to specific diagnoses
Auditory Neuropathy Spectrum Disorder (ANSO): Defining Site of Dysfunction

Summating potential (SP)
Cochlear microphonic (CM)
Action potential (AP)

Auditory brainstem response (ABR)
- Rarefaction versus condensation polarity
- Electrical ABR with questionable auditory nerve integrity

Auditory steady state response (ASSR) if no ABR

DPOAEs from 500 to 8000 Hz

Electrocochleography (ECochG)
- Cochlear microphonic (CM) OAEs
- Summating potential (SP)
- Action potential (AP)

Cortical auditory evoked responses

Acoustic reflexes (ipsilateral and contralateral)

Speech audiometry

Diagnosis of Auditory Neuropathy Spectrum Disorder:
A Complete Test Battery

Electrocochleography (ECochG) Test Protocol (1)

Stimulus Parameters
- Type: Clicks
- Duration: 0.1 ms
- Rate: 7.1/sec or slower as necessary
- Polarities: Alternating for SP and AP
- Intensity: Maximum or lower
- Transducer: Insert
- Masking: Never needed (response is ipsilateral)
Electrocochleography (ECochG) Test Protocol (2)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplification</td>
<td>75,000 or less</td>
</tr>
<tr>
<td>Analysis time</td>
<td>5 or 10 ms</td>
</tr>
<tr>
<td>Sweeps</td>
<td>500 or less</td>
</tr>
<tr>
<td>Filters</td>
<td>10 to 1500 Hz</td>
</tr>
<tr>
<td>Notch filter</td>
<td>Never</td>
</tr>
</tbody>
</table>

ECochG Electrode Options:
The Closer to the Cochlea, the Better

- TipTrode
- Trans-Tympanic Promontory
- Electrode

ECochG is a Near-Field Response (ABR is a Far-Field Response)
Sub-Dermal Needle Electrode for Trans-Tympanic Promontory ECochG Recording


14 subjects (7 male and 7 female) with AN versus 2 normal subjects

AN diagnosed between 3 and 24 months of age

Diagnosis based on large CM potentials and absence of ABR (incl. wave I)

Genetic etiology for 6 subjects

Severe to profound audiometric thresholds for all subjects

All subjects received cochlear implants

ECochG recorded with
- Non-inverting ("active" window "golf club") electrode near round electrode
- Inverting electrode on ipsilateral earlobe

ECochG in AN consistent with:
- Pre-synaptic mechanism (abnormal SP) = good EABR and CI benefit
- Post-synaptic mechanism (normal SP + dentritic potential) but no AP = poor or absent EABR and poor CI benefit

Electrophysiology Procedures in the Diagnosis of ANSD:

Refining diagnosis of "site of lesion"

ANSD: Examples of ECochG Components

Analysis Time 10 ms

Condensation

Rarefaction

CM

SP

N1

N2

Alternating

DP (dentritic potential)
Determining Candidacy for Cochlear Implantation in Auditory Neuropathy Spectrum Disorder (ANSD): Electrically-Evoked Auditory Evoked Responses

Applications of eABR Recordings in Audiology

- Pre-operative verification of cochlear nerve functional integrity
- Assessment of candidacy for cochlear implantation
- Confirm cochlear nerve adequacy in ANSD

Following cochlear implantation

- Binaural different wave for eABR is objective evidence of benefit from bilateral CI
- Document auditory development following CI


Audiologic Characteristics in ANSD: Sample of Recent Literature

- Children with ANSD exhibited differences in central auditory processing.
- Overall, two-thirds of children revealed present P1 CAEP responses.
- Our results suggest that P1 CAEP responses may be a useful tool for recognizing the extent to which neural dysynchrony disrupts cortical development and may be a useful indicator of the extent to which neural dysynchrony disrupts cortical development and a good predictor of behavioral outcome in children with ANSD.
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Clinical Applications of Auditory Late Responses: Documenting Hearing Aid or Cochlear Implant Performance in Patients with ANSD (Anu Sharma, PhD, University of Colorado)

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ANSD: Sites of Lesions and Patterns of Auditory Findings


Auditory Findings (□ = normal; □ = abnormal)

<table>
<thead>
<tr>
<th>Site of Lesion</th>
<th>OAEs</th>
<th>ECochG</th>
<th>ABR</th>
<th>Acoustic Reflexes</th>
<th>EABR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inner hair cells</td>
<td>□</td>
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<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Primary afferent synapse</td>
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<td>□</td>
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<tr>
<td>Auditory nerve</td>
<td>□</td>
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<td>□</td>
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<tr>
<td>Auditory brainstem</td>
<td>□</td>
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</tbody>
</table>

* DP = dendritic potential (broad negative wave)

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Auditory Neuropathy Spectrum Disorder (ANSD): Audiologic Characteristics

- Hearing thresholds variable
  - From normal sensitivity through profound "hearing loss"
  - Rising audiogram configuration in common
- Absent ABR
- ECochG/ABR
  - Cochlear microphonic (CM) and summating potential (SP) present
  - Reversal of polarity of CM when recorded with condensation vs. rarefaction click signals
- OAEs present (often normal)
  - Lack of OAE suppression with noise (efferent abnormality)
- Fluctuating auditory status (may be temperature dependent)
- Poor temporal coding and processing
- Very poor word recognition scores, even in quiet
- Noise severely disrupts speech perception
ANSD: Audiologic Management

- Close monitoring every three months until behavioral audiometry is complete; consider videotaping all observations
- Monitor OAEs
- Referral to other disciplines
- Hearing aids on trial basis with evidence of either:
  - Elevated pure tone or speech thresholds
  - Behavioral observation consistent with abnormal sensitivity
- FM technology:
  - Personal FM system (e.g., Phonak iSense)
  - With hearing aids
  - With cochlear implants
- Alternative communication strategies:
  - Cued speech
  - Signing options (e.g., www.BabySigns.com)

Thank You!
Questions?
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