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Auditory Neuropathy Spectrum Disorder: Mechanisms, Genetics and Outcomes

Linda J. Hood, Ph.D.
Auditory Neuropathy Spectrum Disorder: Mechanisms, Genetics and Outcomes

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Learning Objectives

• List four key recent articles regarding auditory neuropathy spectrum disorder (ANSD) with implications for audiology clinical practice.
• Describe the key findings from four recent articles regarding auditory neuropathy spectrum disorder (ANSD) with implications for audiology clinical practice.
• Explain the implications for audiology clinical practice from the articles presented on auditory neuropathy spectrum disorder (ANSD).

Auditory Neuropathy (AN)
Auditory Neuropathy/Dys-synchrony (AN/AD)
Auditory Neuropathy Spectrum Disorder (ANSD)

- Clinical Presentation
  - Problems listening in noise, fluctuation, delayed speech/ language development
- Physiologic Responses
  - Hair Cell Responses
    - Present otoacoustic emissions, cochlear microphonics
  - Neural Responses
    - Absent, highly abnormal auditory brainstem responses, middle ear muscle reflexes
- Behavioral Responses
  - Variable pure tone thresholds, speech recognition
Underlying Mechanisms

Possible sites of abnormality:

- Inner hair cells
  - Critical for sound discrimination while OHCs improve detection
- Synapse at inner hair cell - VIIIth nerve
- VIIIth nerve

Genetics and ANSD

- Affected siblings or other family members
  - Inheritance patterns: autosomal recessive, autosomal dominant, x-linked, mitochondrial
- Non-syndromic ANSD
  - OTOF – otoferlin
- ANSD as part of a syndrome
  - Charcot-Marie-Tooth disease
  - Friedreich ataxia

Some candidates (gene name, loci or protein product):

- OTOF
- OPANK
- Xq23-27.3 (AUNX)
- 13q14-21 (AUNA1)
- 12SrRNA (mtDNA)
- Cx26 (GJB2), Cx30 (GJB6)
- Cx29, Cx31 (GJB3), Cx32 (GJB1)
Inconsistent auditory responses, difficulty especially in noise. Audiograms may fluctuate. ABR desynchronized, middle-ear muscle reflexes absent. Speech and language delays; communication difficulty.

No observable delays or auditory complaints; discovered by first MEMRs or ABR

Total lack of sound awareness

Patient Variation: A Continuum of ANSD

Adapted from Berlin, Hood, Morlet et al., IJA, 2010

Auditory neuropathy – neural and synaptic mechanisms

Tobias Moser and Arnold Starr

Institute for Auditory Neuroscience and Inner Ear Lab, University of Gottingen, Germany

Center for Hearing Research, University of California, Irvine, California, USA

A review...

- The terms AN, AN/AD, ANSD have classically encompassed abnormal function in the regions of the sensory IHCs, IHC ribbon synapses or spiral ganglion neurons.

- Advances in physiological and psychophysical characterization, and molecular genetics studies, facilitate differentiation of disrupted activity at the level of the auditory nerve (true "auditory neuropathy") from disordered IHC ribbon synapse function (termed "auditory synaptopathy").

A review...

- This review article (1) summarizes recent insights into function and dysfunction of inner hair cell ribbon synapses and (2) discusses disease mechanisms primarily affecting spiral ganglion neurons.

- Ribbon synapses: Highly specialized synapses between IHCs and spiral ganglion neurons, at the presynaptic active zone, that mediate neurotransmitter release.

Figure 2, Moser and Starr, 2016
Why it matters...

- Understanding the sources of abnormal findings on audioligic and vestibular tests with greater precision allows more accurate interpretation and promotes more informed management.

Neural representation of signals can be affected by loss of neurons, demyelinating disease, poor input from IHCs or through the synapse, or combinations of these.
Ribbon synapses of the IHCs are highly specialized for encoding of sound with sub-millisecond temporal precision.

- Mechanisms of auditory synaptopathy and neuropathy
  - Genetics and auditory synaptopathy
    - OTOF gene codes for otoferlin
      - Expressed in sensory IHCs and associated with synaptic function.
      - Some patients with OTOF mutations have a form of ANSD now associated with synaptopathy.
      - Some patients with OTOF mutations display a temperature sensitive form of ANSD.
      - OTOF mutations are also associated with autosomal recessive SNHL (DFNB9)
  - We will talk more about OTOF in Article 2.
• Mechanisms of auditory synaptopathy and neuropathy
  
  – Genetics and auditory neuropathy
    • Mutations in the OPA1 (optic atrophy 1) gene
      – Hearing loss typically follows onset of visual impairment with slow progression.
      – Patients with OPA1 mutations will be discussed in Article 3.
    • Hereditary motor sensory neuropathies (HMSN)
      – Mutations in MPZ gene that codes for myelin protein zero in Schwann cells associated with ANSD.
      – Charcot-Marie-Tooth disease (CMT), Friedreich ataxia (FA)
      – Patients with CMT and FA will be discussed in Article 4.

Why is this important and does it matter clinically?

- Understanding sources underlying loss of temporal precision (synchrony) and inaccurate neural representation of auditory signals enhances understanding of some forms of ANSD.

- Identifying specific genetic mutations associated with ANSD provides better understanding of underlying mechanisms and etiology.

- This information provides a basis for more accurate evaluation and management of patients with ANSD.
Audibility, speech perception and processing of temporal cues in ribbon synaptic disorders due to OTOF mutations

Rosamaria Santarelli, Ignacio del Castillo, Elona Cama, Pietro Scimemi, Arnold Starr

Department of Neurosciences, Audiology and Phoniatrics Service, University of Padova, Padova, Italy


What they asked...

• What are the audiological and electrophysiological findings in children with congenital profound deafness related to mutations in the OTOF gene?

• What are the outcomes of management with cochlear implants in these children?
Why it matters...

- Clinical findings and outcomes may differ depending on the underlying mechanisms and whether the site is pre- or post-synaptic.

Some background: Loudness adaptation in patients with pre-synaptic and post-synaptic ANSD

A study by Wynne et al. (2013) showed greater loudness adaptation in temperature-sensitive ribbon synapse disorder than post-synaptic neural AN.

ABRs showed similar adaptation effects.

Figure 1, Santarelli et al., 2015 after Wynne et al., 2013
What Santarelli et al. did...

- Subjects: 8 children with OTOF mutations and characteristics of ANSD (age at test 4 mos-2 yrs)
  - Truncating mutations (n=4)
  - Truncating and non-truncating mutations (n-3)
  - Non-truncating mutations (n=1)

- Audiologic tests:
  - Pure-tone thresholds
  - OAEs
  - ABRs
  - ECochG

- All children fit with hearing aids.
- All children ultimately received cochlear implant.

What they did...

Transtympanic Electrocochleography (ECochG)

ECochG (particularly transtympanic) provides accurate information about:

- CM – cochlear microphonic; primarily reflecting OHC transduction
- SP – summating potential; primarily reflecting summed IHC receptor potential
- CAP – compound action potential; reflecting synchronized firing of spiral ganglion neurons

Figure 1a, Moser and Starr, 2016
What they found...

Subject #2 – Two truncating mutant OTOF alleles

Figure 3, Santarelli et al., 2015

What they found...

Cochlear potentials in response to clicks at descending stimulus intensities

CM present

SP present and neural response (CAP) affected; prolonged negative response

Figure 5, Santarelli et al., 2015
What they found...

Hearing Thresholds in Children with OTOF mutations

Figure 4, Santarelli et al., 2015

- Six children with OTOF mutations were implanted.
  - MRI and CT scans were normal.

- All children showed excellent improvement within 3 months of CI use.

- Speech perception scores with CI ranged from 90-100% (mean=95.8%)
  - Administered after 3 years of age and CI use of 1-1.5 years.
What they found...

Post-CI eCAPs had typical morphology, consistent with preserved nerve fiber excitation and conduction.

Why is this important?… And matter clinically…

- Patients with this form of pre-synaptic ANSD show preserved neural function.
  - Observed by presence of electrically evoked compound action potentials.

- Based on these findings, patients with presynaptic AN due to OTOF mutations can be expected to have successful outcomes with CI.
**OPA1-related auditory neuropathy: site of lesion ad outcome of cochlear implantation**

Rosamaria Santarelli, Roberta Rossi, Pietro Scimemi, Elona Cama, Maria Lucia Valentinno, Chiara La Morgia, Leonardo Caporali, Rocco Liguori, Vincenzo Magnavita, Anna Monteleone, Ariella Biscaro, Edoardo Arslan, Valerio Carelli

*Department of Neurosciences, Audiology and Phoniatrics Service, University of Padova, Padova, Italy*


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**What they asked...**

- What are the site of lesion and pathophysiological mechanisms related to hearing loss in patients with Dominant Optic Atrophy (DOA) carrying mutations in the *OPA1* gene?
  - Hearing loss is the second most prevalent feature after optic atrophy

- What are the outcomes of management with cochlear implants in these children?
Why it matters...

- *OPA1* gene mutations result in post-synaptic auditory neuropathy.

- Clinical findings and outcomes may differ depending on the underlying mechanisms and whether the site is pre- or post-synaptic.

What they did...

- **Subject groups:**
  - 11 patients with *OPA1* mutations including haploinsufficiency (*OPA1-H*: 13-79 years; 9 of 11 had normal hearing)
  - **10 patients with *OPA1* missense mutations** (*OPA1-M*: 5-58 years)
    - 20 subjects with normal hearing
    - 19 subjects with cochlear hearing loss

- **Tests, focusing on *OPA1* missense mutation patients:**
  - Behavioral thresholds, speech perception
  - Physiological: OAE, ABR, ECochG
  - Absent ABRs

- Hearing aids and cochlear implants
Audiological test results – *OPA1-M* patients

- Pure-tone thresholds ranged from normal to profound with most patients falling in the mild to moderate hearing loss range.
- OAEs present in 8 of 10 patients.
- MEMRs absent in 9 of 10 patients.
- ABRs absent bilaterally in 15 ears; present but abnormal in 3 ears; normal in both ears in one patient.
- Two patients complained of tinnitus and vertigo.

ABR test results: *OPA1-M* patients show absent or highly degraded responses.

Figure 2, Santarelli et al., 2015
Cochlear microphonic results – OPA1-M patients

- CMs have higher amplitude in OPA1-M patients.
- May be related to decreased efferent activity secondary to abnormal auditory nerve activation.

Figure 3, Santarelli et al., 2015

Cochlear responses (SP, CAP) – OPA1-M patients

SP latency and amplitude similar to NH controls, consistent with IHC preservation.

CAP shows prolonged negativity.

Figure 4, Santarelli et al., 2015
Speech perception reduced in all but one OPA1-M patient.

Articulation gain curves
Classified by PTA and compared to NH subjects

Cochlear implant: Pre- and post-CI speech recognition in quiet and in noise in OPA1-M patients

Speech recognition scores improved post cochlear implant for all except one patient (not shown).
Cochlear implant: Electrically evoked ABRs varied among OPA1-M patients.

No eCAP in 5/6 subjects; present eABR seen in most subjects.

Present eCAP and eABR seen in one subject

One subject had no eABR.

Why is this important?... And matter clinically...

• ANSD patients displaying OPA1-M mutations show variable test results.

• Outcomes with CI are generally positive; all but one patient demonstrated improvement in speech recognition.

• Present eABR and absent eCAP suggest involvement of the distal portion of auditory nerve fibers.
  – Electrical stimulation through the cochlear implant may bypass abnormal function localized to the terminal dendrites.
Binaural speech processing in individuals with auditory neuropathy


The University of Melbourne, Department of Audiology & Speech Pathology, Parkville, Melbourne, Australia

Neuroscience 226, 227–235 (2012)

What they asked...

- The goals of this study were to:
  - Characterize binaural auditory processing in two types of AN, one axonal (Friedreich ataxia; FA) and one demyelinating (Charcot-Marie-Tooth disease 1A; CMT).
  - Evaluate the relationship between degree of deficit and overall clinical severity.
  - Track binaural processing changes over time.
Charcot-Marie-Tooth disease

- Most common inherited peripheral neuropathy
  - Progressive degenerative disorder of the peripheral nervous system
    - Results in muscle weakness of the distal extremities
  - Hearing affected in some but not all CMT patients
    - Symptoms typically present in late adolescence or early adulthood
    - Bilateral, progressive, characteristics consistent with AN
- Inheritance: Variable patterns and multiple subtypes
  - CMT 1: peripheral myelin protein disorder; reduced neural conduction
  - CMT 2: axonal defect; nerve impulse transmission
  - Abnormal protein production interferes with the axon’s ability to transmit nerve impulses and/or disturbs myelin production.

Friedreich ataxia

- Progressive disorder of nervous system and muscles
  - Degeneration of nerve tissue in spinal cord and nerves that control limb movement
  - Heart disease, hearing loss, dysarthria, reduced mobility
- Hearing Loss
  - Mild to profound
  - Unilateral or bilateral
  - Usually progressive
- Autosomal recessive, mutation of the gene frataxin
  - Most frequent mutation: abnormal expansion of trinucleotide GAA repeat
  - GAA codes for the amino acid, glutamic acid
Why it matters...

- AN patients with different underlying causes/mechanisms may perform differently on binaural listening tasks.
- Very little work has been done to date to characterize these responses in AN patients.

What they did...

- Subjects:
  - 23 subjects with genetically confirmed Friedreich ataxia
  - 12 subjects with Charcot–Marie–Tooth disease type 1A
- Tests performed:
  - Psychophysical evaluation of intensity discrimination and temporal resolution.
  - Binaural speech perception assessment using the Listening in Spatialized Noise test.
  - Age, gender and hearing-level-matched controls tested.
What they found…

Spatial hearing is reduced for both FA and CMT patients compared to matched control subjects.

FA: Spatial advantage = 7.6 dB (Controls = 11.9 dB)
CMT: Spatial advantage = 8.3 dB (Controls = 11.5 dB)

What they found…

Relationship between spatial hearing and severity of disease

Spatial advantage and FARS score were highly correlated ($r = -0.81$, $P < 0.001$).

CMT Neuropathy Score was significantly correlated for spatially separated speech and noise ($DV90^\circ$: $r = 0.71$, $P < 0.01$; $SV90^\circ$: $r = 0.73$, $P < 0.01$) and spatial advantage: $r = -0.84$, $P < 0.001$. 
What they found…

11 FA subjects retested 2-3 years later.

Performance was poorer for spatial separation and spatial advantage on the second test, and was consistent with changes in FARS score.

![Figure 6, Rance et al., 2012](image)

Change in spatial advantage plotted against change in FARS score ($r = 0.87, P < 0.002$).

Why is this important?…

- Provides evidence that temporal distortion in the auditory nerves of individuals with AN can disrupt integration of binaural difference cues.
- This can affect ability to use spatial information/interaural cues to improve speech perception in background noise.
- The spatial listening measure appears sensitive to progression of disease.
Questions?