Sound for a Young Generation
2nd European Phonak Conference

Auditory Neuropathy:
Update and Recent Findings

Yvonne S. Sininger PhD Professor,
Division of Head & Neck Surgery,
UCLA David Geffen School of Medicine
Outline

• Brief Overview

• Newest Information:
  ASSR in patients with AN
  Psychophysics of Hearing
  Related Genetic Mutations
  Infant Numbers/Risk Factors
  Use of CI with Moderate Hearing Loss
"Auditory Neuropathy"

**Typical Profile**

- Hearing Loss (mild-profound) - sensorineural pattern
- Absent or severely abnormal ABR (regardless of hearing)
- Cochlear Microphonic present in ABR recording (larger than normal)
- Otoacoustic Emissions present but sometimes disappear
- Poor speech perception (relative to sensory loss of the same degree)
- No Acoustic (middle ear muscle) Reflex
Age: 27 years

Speech Discrimination:
Right Ear = 40%
Left Ear = 64%

Tympanometry:
WNL Bilaterally

Ipsilateral Acoustic Reflex
Thresholds:
Absent or Elevated Bilaterally

Right Ear
Left Ear

Auditory Brainstem Response

Click 80 dBnHL 11/s Insert Earphones
Synchrony happens when the timing of spikes is matched across a population of nerve fibers. In the auditory system the timing is synched with the initiating sound across primary auditory neurons. Dysynchrony is when activity across nerve fibers does not have the same timing pattern as the auditory stimulus. This will happen when conduction properties of the nerve are altered.
ASSR (with fast modulation rates ~90 Hz) does not predict behavioral thresholds in patients with Auditory Neuropathy.

~70-100 dB threshold for all Patients- Could be detection of Cochlear Microphonic or stimulus artifact.

Rance et al.
Psychoacoustics of Auditory Neuropathy

Gap Detection

Michalewski et al 2005
Half of the AN subjects had Passive and Active Cortical Responses (2/3 had active).

In subjects with a response, EP Gap Thresholds corresponded well to Psychophysical thresholds.

4ms ↔ 30 ms
Psychophysical GDT
Psychoacoustic Measures Indicate a Primary Temporal Processing Disorder

Lateralization from Timing Cues is Disrupted


*J Neurophysiol* 93 (6):3050-3063
Mild disorder of Intensity Discrimination
Low frequency disorder of Frequency Discrimination

Non-Significant

Reflects a timing/place relationship


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- Study of children AN (4 - 10.7 years) SNHL and controls.
- Some methodological differences with Zeng.
- Most results similar some discrepant
- Poor temporal resolution as measured by TMTF (TMTF correlates with speech perception)
- Near Normal Frequency Resolution
  used a notched noise technique
- Poorest AN subjects (speech) show poor frequency discrim
- Considerable inter-subject variability
Rance et al (as Zeng and others) find TMTF a good predictor of speech perception.
Genetics of Auditory Neuropathy

**Syndromic**
- Autosomal Dominant Spino-Cerebellar Ataxia (Friedreich’s)
- Hereditary Motor and Sensory Neuropathy (HMSN)
- Charcot-Marie-Tooth  CMT-I (myelin) CMT-II (axonal)
- Autosomal Dominant, Autosomal Recessive or X-linked
- Refsum’s Disease

**Non-Syndromic**
- Autosomal Dominant /AUNA-1/
- Autosomal Recessive /DFNB-9/OTOF


Evaluated 72 members of generations 4-7.

Physiology unknown

Non-Syndromic Autosomal Dominant /AUNA-1/

Hearing Loss Progresses (onset 7-45 years), OAEs Disappear
Three Members have CI with good performance
No evidence of other Peripheral Neuropathy

Protein or mechanism unknown
No post mortem information

• Myelin Protein Zero (MPZ) associated with CMT

**MPZ Family with Auditory Neuropathy**

Affected family members show:

* Evidence of generalized peripheral nerve disorder
* Variable degree of hearing loss
* Typical AN ABR findings
* OAEs (gone in one of three subjects)
Hair cells were found to be intact but as shown poor nerve survival and evidence of myelin breakdown.

**Fig. 8** Auditory nerve adjacent to brainstem from AN subject (A) and aged-matched control (B) (osmium tetroxide, ×400). High power (×1500) of auditory nerve (C) and sural nerve (D) from the AN subject. The arrows are directed to thinly myelinated fibres in both nerves reflecting incomplete remyelination.

- Patients with HMSN-1a with duplications on chromosome 17p11.2 have congenital loss without abnormal progression.
- Patients with HNPP (Hereditary neuropathy with liability to pressure palsies) with deletion and frameshift mutations show late onset hearing loss with rapid progression.


**Phenotype:**

- Prelingual deafness, severe to profound, OAE present, vestibular function normal.

Called Non-syndromic, recessive auditory neuropathy (NSRAN)

**Location:** Chromosome 2p 22-23  gene: OTOF

**Protein Otofelin:** Found in IHC, aids in vesicle transport.
37 Subjects with two mutations of the OTOF Gene

- 24 cases were familial and 13 sporadic
- All hearing losses were onset < 1 year
- Flat audiograms >90 dB  No ABR
- 21 cases were evaluated by TEOAE.
  - Clear, bilateral response in 6
  - Unilateral TEOAE in 4
  - One with bilateral response at 19 months gone by 26 months
  - 10 with No OAEs.
- 10 subjects implanted with good success

Otoferlin involved in vesicle-membrane fusion.

OTOF mutations can explain 3.5% of non-syndromic deafness.

Bilirubin and the auditory system.
Shapiro, SM and Nakamura H

The auditory system is highly **sensitive to bilirubin toxicity**. Damage to the auditory nervous system includes auditory neuropathy or auditory dyssynchrony and auditory processing problems which may occur with or without deafness, hearing loss. Auditory dysfunction may occur in children with or without other signs of classical kernicterus. Bilirubin selectively damages the brainstem auditory nuclei, and **may also damage the auditory nerve and spiral ganglion containing cell bodies of primary auditory neurons**. The inner ear, thalamic and cortical auditory pathways appear to be spared. **Noninvasive auditory neurophysiological tests such as the auditory brainstem response (ABR) or brainstem auditory response (BAER) play an important role in the early detection of bilirubin-induced auditory and central nervous system dysfunction in the neonate.**
• Sampled 477 NICU Infants Screened with ABR/OAE
• 115 (24.1%) demonstrated an AN pattern
• Individually, factors distinguishing the AN from other NICU patients include Hyperbili-rubinemia, vancomycin and furosemide while no factors distinguished the groups using logistical regression.
34 Year old patient with AN since 10 years of age. Speech Discrimination 0% left ear, 15 % right ear. Implanted in Right Ear. Dramatic improvement in speech perception. Post-operative electrical ABR present.
Summary of New AN Findings

- ASSR thresholds (using high frequency modulation) are not related to hearing but may reflect CM.
- Temporal processing, low frequency localization and frequency discrimination are impaired: results are widely variable.
- Genetic information related to syndromic and non-syndromic AN can aid in determination of physiology.
- High numbers of cases of infants can be expected especially infants enrolled in the NICU.
- Adults with moderate hearing loss due to AN have received CIs with good results.
Thanks for Listening