Towards a better understanding of aetiology and typology of Auditory Neuropathy Spectrum Disorder

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Speculate on (not necessarily answer) the following questions:

- What is the epidemiology and aetiology of ANSD in neonates?
- Could knowing the aetiology of ANSD help with ‘phenotyping’?
- Could ‘phenotyping’ help in management decisions?
What is the epidemiology of ANSD in different populations?
# Prevalence in PCHL Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vohr et al 2001</td>
<td>Universal screening</td>
<td>1.80</td>
</tr>
<tr>
<td>Berlin et al 2000</td>
<td>1000 HI infants</td>
<td>8.70</td>
</tr>
<tr>
<td>Kraus et al 1984</td>
<td>48 HI infants</td>
<td>14.58</td>
</tr>
<tr>
<td>NHSP Evaluation 2004</td>
<td>169 HI infants</td>
<td>10.1</td>
</tr>
</tbody>
</table>
newborns: prevalence in at-risk population

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein et al 1996</td>
<td>special care nursery</td>
<td>4.00</td>
</tr>
<tr>
<td>Psarommmatis et al 1997</td>
<td>intensive care unit</td>
<td>1.96</td>
</tr>
<tr>
<td>Rance et al 1999</td>
<td>“at-risk” infants</td>
<td>0.23</td>
</tr>
<tr>
<td>NHSP Evaluation 2004</td>
<td>babies in NICU for ≥48 h</td>
<td>0.2</td>
</tr>
</tbody>
</table>
aetiology in SCBU newborns

- prematurity and/or low birth weight
- hyperbilirubinaemia
- anoxia/hypoxia
- ...

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• **Kernicterus** often occurs at lower bilirubin concentrations in premature newborns as compared with term newborns.

• A higher sensitivity to **hypoxic-ischemic damage** has been observed in premature infants.
hyperbilirubinaemia

hyperbilirubinaemia

- total serum bilirubin (TSB): 20 mg/dL
- peak total serum bilirubin: 16 mg/dL
- unbound bilirubin
  - term babies: 1 to 2 mg/dL
  - preterm 0.5 mg/dL (Amin et al 2001)
Where does bilirubin damage the auditory system?

– inner ear: NO
– spiral ganglion and auditory nerve: YES
– brainstem auditory nuclei: YES
– thalamus and auditory cortex: NO

anoxia/hypoxia

- chronic mild hypoxia selective inner hair cell loss:
  - human temporal bone (Amatizzi et al 2001)
  - animal studies (Mazurek et al 2003)
prevalence in well-baby population

Low???

1:500,000 (Mehl 2002)

1:200,000 (Australian unpublished data 2005)
prevalence in well-baby population

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1:200,000 (Australian unpublished data 2005)

...

But:
1:5,700 (Owen et al 2008)
prevalence in well-baby population

Low???
1:500,000 (Mehl 2002)
1:200,000 (Australian unpublished data 2005)

But:
1:5,700 (Owen et al 2008)

And:
**ANSD in well-baby population**

(Sininger & Oba 2001)

**Table 2-1.** Patients with onset of auditory neuropathy before age 2 years, grouped by family history and other neonatal risk factors.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Family or Genetic History</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>2</td>
</tr>
<tr>
<td>Prematurity</td>
<td>1</td>
</tr>
<tr>
<td>Multiple risk factors</td>
<td>0</td>
</tr>
<tr>
<td>No other risk factors</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
</tr>
</tbody>
</table>
aetiology in well-baby population

- heredity:
  - autosomal recessive isolated (Varga et al 2003, Delmaghani et al 2006)
  - syndromes e.g. Waardenburg (Pau et al 2006)

- cochlear nerve deficiency (Buchman et al 2006)
  - developmental aplasia/agenesis

- tumor or cyst (e.g. intracranial arachnoid cyst Boudewyns et al 2008)
autosomal recessive isolated ANSD

• **DFNB9** (Varga et al 2003)
• **DFNB59** (Delmaghani et al 2006)
• locus: DFNB9 gene: OTOF
• mutations in the gene encoding otoferlin
• primary lesion at the level of the inner hair cells (IHC)

(Varga et al 2003)
Rodriguez-Ballesteros et al (2008) suggest that mutations in OTOF are a major cause of isolated ANSD

– of patients with ANSD 55-87% (Rodriguez et al 2008)

– 4.4% of recessive familial or sporadic cases of deafness in the Spanish population autosomal recessive isolated HL (Migliosi et al 2002)
• locus: DFNB59 gene: PJFK
• mutations in the gene encoding pejvakin
• primary lesion neurons in the spiral ganglion and the brainstem auditory nuclei

(Delmaghani et al. 2006)
Is transient (neonatal) ANSD worth talking about?
• ABRs have been reported to recover (or improve)
• ABR recovery (or improvement) may happen by up to as late as two years of age (Madden et al 2002)
• perceptual ability may improve even when ABR remains abnormal
prevalence of transient ANSD

• 24% in our pilot data
• 65% (Psarommmatis et al 2006)
the reported aetiological/risk factors:

- hydrocephalus (Russell et al 2001)
- anoxia (Attias et al 1990, 2007)
- metabolic toxic and/or inflammatory factors (Alexander et al 1995)
- genetic factors
  - familial isolated delay of auditory maturation (Neault & Kenna 2004)
  - syndrome such as maple syrup urine disease (Spankovich et al 2007)
  - coexisting alongside delayed visual maturation in the absence of any known risk indicators has been described (Aldosari et al 2003)
low birth weight and neuromaturation

• Changes in myelination
• Changes in synaptic efficiency
• Other???
Phenotyping of ANSD
At birth:
Normal OAEs
Absent ABR

Prognosis???

Normal auditory function

Total lack of sound awareness

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At birth:
Normal OAEs
Absent ABR

by 2 yrs

Normal ABR

by 2 yrs

Absent ABR

Normal hearing thresholds

Normal speech perception

Speech perception worse than expected from audiogram

Elevated hearing thresholds

Speech perception matches audiogram

Speech perception worse than expected from audiogram

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Speech perception worse than expected from audiogram
take-home messages

• ca 10% of all children with PCHL have ANSD
• 0.2% of all NICU babies have ANSD
• more research needed to understand ANSD in well-baby population
• a proportion of babies identified with ANSD at birth will recover
• knowing aetiopathology may potentially help us choose more appropriate management options
Thank you!