Auditory Neuropathy – Does cCMV Play Role?

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Auditory Neuropathy

Retrocochlear structures
Importance of identifying AN verses cochlear sensory hair cell dysfunction


- AN results in impaired processing of acoustic temporal cues which are critical for sound localization, speech discrimination & signals in background noise
- Speech discrimination scores do not mirror pure tone audiometry thresholds
- **AN is common in hearing loss (1:7000) 8-10% all congenital hearing losses**
- Associated with many neurometabolic & other conditions eg mitochondrial relevant in both early diagnosis & disease progression/treatment
- Type of hearing habilitation will be impacted, both hearing aids & cochlear implantation decisions
- Amplification not helpful in the majority
- FM units with teacher microphone and child receiver helps reduce the effect of background noise
- Cochlear Implant has become the treatment of choice but predicting which children will benefit is not fully clear
Reports of AN in cCMV to date are few

**Study 1:**

**Study 2:**
Royackers L et al. Hearing status in children with congenital CMV up to 6 years audiological follow up. Int J Paediatr Otorhinolaryngology, 2011, 75,376-382. **One case AN described diagnosed at 5 months**

**Study 3: Case Report:**
Baerts W, van Straaten HLM. Auditory neuropathy associated with postnatally acquired cytomegalovirus infection in a very preterm infant BMJ 2010. Confirmed at 6 weeks of age. Normal CT, received cochlear implant with good outcome. Proposed infected breast milk

**Study 4:**
Coenraad S, Goedegebure A et al. Risk factors for Auditory Neuropathy disorder in NICU Infants Compared to Normal Hearing NICU Controls. Laryngoscope, 121: 852-855, 2011. 9/103 had bilateral AN, no controls or AN had CMV
Diagnosis of Auditory Neuropathy

- Auditory Brainstem Response waveforms (ABR)- Starr 1978
- Cochlear microphonics-Dallas & Cheatham 1976
- Auditory Steady State Response (ASSR) 1980s
- Otoacoustic emissions (outer hair function proxy measure) Kemp 1978
- Tympanometry (middle ear pressure)

- Auditory neuropathy cannot be distinguished where there is a profound cochlear loss
The normal transient (click) auditory brainstem response (ABR)
Generators of the ABR within the auditory pathway

Wave I - 8th nerve (close to cochlea)
Wave II - 8th nerve (proximal)
Wave III – Cochlear nucleus
Wave IV – Superior olive
Wave V – Lateral lemniscus
ASSR/Behavioural Hearing Threshold

Behavioural Hearing Threshold (dBHL)

ASSR Threshold (dBHL)

1 kHz
4 kHz
Pre-synaptic: inner hair cell (hypoxia)

Pre-synaptic: nerve terminal synapses with inner hair cells (genetic mutation [OTOF])

Post-synaptic: auditory dendrites (genetic mutation OPA1)

Post-synaptic: spiral ganglion cells (kernicterus)

Post-synaptic: myelinated axons (auditory nerve hypoplasia / FRDA / CMT)

Post-synaptic: auditory brainstem (acoustic neuroma / MS)
Mechanisms Producing the AN Result Pattern

- **Deafferentiation**: reduction in the number of activated auditory nerve fibres

- **Dyssynchrony**: disruption of the timing of auditory nerve activity
Deafferentiating Neuropathy

Control: 21 yrs

FRDA: 18 yrs

FRDA: 19 yrs

FRDA: 21 yrs

0.75 µV/Div

ms

I

III

V

I

III

V

*  *

0  2  4  6  8  10  12  14
Neural Dyssynchrony

Control: 38 yrs

CMT1: 28 yrs

CMT1: 33 yrs

CMT1: 38 yrs

0.5 µV/Div

ms
Patient 1 Infant with cCMV showing resolved AN on electrophysiology testing suggesting deafferentiating process

- 16 year old mother seroconversion with flu like illness in 2nd trimester
- Male infant born 6 hour labour, NVD 37.3 weeks gestation
- 2.490kg, head circumference 32cm
- Apgars 5 at 1 minute, 9 at 5 minutes
- Cord blood CMV PCR positive, urine culture positive
- Initial raised ALP 377, GGT 319, ALT 57 with neutropenia and monocytosis
- AN day 6 diagnosed
- Commenced 6 month course Valgancyclovir day 6 after the ABR
- MRI normal brain and inner ear structures
- Normal echocardiogram
- Normal eye examination
- **Negative Guthrie CMV**
Patient 1: 6 days

0.5 µV/Div

ms

0 2 4 6 8 10 12 14

Left: 40 dBnHL
Left: 20 dBnHL
Right: 90 dBnHL
Right: 80 dBnHL
Right: 60 dBnHL
Right: 40 dBnHL
Patient 1: 6 days
(Right Ear: unipolar stimuli)

- 90 dBnHL: Compression
- 90 dBnHL: Rarefaction
- 80 dBnHL: Compression
- 80 dBnHL: Rarefaction

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- 0.5 µV/Div
- 0 ms
- 14 ms
- CM

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Emerging ABR: Right ear (90 dBnHL)

- 6 days
- 7 weeks
- 5 months
- 6 months
- 8 months

Diagram showing ABR waveforms for different time periods:

- **0.5 µV/Div**
- **ms**

Waveform peaks labeled as III and V.
Deafferentiating Neuropathy

Control: 21 yrs

FRDA: 18 yrs

FRDA: 19 yrs

FRDA: 21 yrs

0.75 µV/Div

ms

0 2 4 6 8 10 12 14

I  III  V

I  III  V

*  *

I  III  V
6 months

Right A.C. – single polarity click
Patient 2

- 11.7 year old boy born 41 weeks normal pregnancy, NVD, birth weight 3kg.
- Day 2 dusky episode in postnatal ward
- Petechial rash, hepatosplenomegaly, systolic murmur
- Urine CMV PCR >15 million copies/ml
- Failed infant hearing screen
- Commenced Ganciclovir day 4 for one week
- Testing day 10 ABR absent right (110dBnHL), left (107dBnHL), ASSR right severe-profound at 500Hz & 1000Hz , left profound 1000Hz
- MRI day 3 extensive white matter signal most marked in anterior temporal lobes and periventricular regions with extensive polymicrogyria
- CT 6 months normal inner ear structures no calcification
- MRI 6 months normal 7th & 8th nerves, severe widespread polymicrogyria, subcortical & deep white matter abnormalities
Asymptomatic > Symptomatic baby
Mixed largely dystonic cerebral palsy (recent Botox treatments)

Specific learning difficulties, particularly Maths concepts

FSIQ 96 (Average) but with scattered profile: Processing Speed 4% (includes auditory processing & working memory)

Impulsivity

Considerable oromotor delay in speech & saliva control
Patient 2: 6 weeks

Left Alt Clicks: 100 dBnHL
Right Alt Clicks: 100 dBnHL
Right Compression Clicks: 100 dBnHL
Right Rarefaction Clicks: 100 dBnHL
Patient 3

- Normal pregnancy and 40 week birth no risk factors
- Unilateral AN diagnosed at 3 weeks
  - Absent ABR/present cochlear microphonic /present otoacoustic emissions
- 10 months
  - MRI: right cochlear nerve normal, left cochlear nerve hypoplasia
Patient 3

- **12 months**
  - Normal physical milestones
    - walking without support

- **Hearing**
  - Right ear: normal sound detection thresholds
  - Left ear: severe-profound loss

- **11 months**: Hearing aid fit to left ear
  - Not well tolerated after 4 weeks
    - Could reflect poor hearing on that side or AN-related sound distortion (or just doesn’t want anything in her ear)
  - About to receive remote microphone (FM) device – fit to the better (left) ear to maximise listening at day-care
Patient 3: Auditory Brainstem Response

Right Alt Clicks: 50 dBnHL

Right Alt Clicks: 20 dBnHL

Left Compression Clicks: 100 dBnHL

Left Rarefaction Clicks: 100 dBnHL
Patient 3: Left Ear Otoacoustic Emissions

![Graph showing response amplitude (dB) vs frequency (Hz) for left ear otoacoustic emissions. The graph displays X markers at specific frequencies indicating presence of emissions, and squares representing noise levels.](image-url)
Patient 3
Behavioural Audiogram (12 mo)
Patient 4 – Video frontal seizures

20 year old woman
Mother unwell during first and second trimesters
No abnormalities noted with her as a neonate
No hearing screening program
Presented at 8 months gross motor delay
Microcephaly
MRI major cortical polygyria & calcification mainly frontotemporal
Hearing loss – felt to be cortical
Not implanted so Auslan dependant
Microphthalmia no vision in left eye
Patient 4 – MRI pictures
Children with Auditory Neuropathy recruited following referral by audiologists and clinicians. Royal Victorian Eye & Ear Hospital ethics approval obtained. Parental consent given for retrospective newborn Guthrie card CMV testing. Further audiology testing done at The Melbourne University Audiology Department.

Total cohort planned to enrolment 100 individuals with auditory neuropathy
- 48 consents
- 28 samples received
- 7 interstate or overseas
- 13 yet to be tested
Results of Guthrie tests

- N= 28 tested
- Patient 1 had a false negative
- 9 had no risk factors (30%) CMV not detected
- 2 positive for CMV PCR (11%)
- 16 had risk factors (59%) and CMV not detected, many children had a combination:
  - Anatomical 3
  - Hypoxia 6
  - Genetic 3
  - Prematurity 6, 3 ELBW
  - Jaundice 10, including one baby with 3 exchange transfusions but no other factors
  - Antibiotics (Gentamycin & Vancomycin)
  - Toxoplasmosis
Mechanisms of Pathogenesis

- Interfere with cell cycle
- Modify apoptosis
- Modify immune response, particularly in susceptible host (pregnant mother & premature infant)
- Placental injury with vasculitis
- Damage to gene structure in the host
- Importance of viral load, modified by antiviral treatment (Valgancyclovir)
- Viral latency and activation
Potential pathogenesis- chromosomal breakage

- CMV effect on chromosomal breakage:
  - 1q42 region (DFNA7), autosomal non syndromal progressive SNHL
  - 1q21 region (USH 2A) progressive vision loss & SNHL
  - 1q23.3 region (between DFAN7 & DFNA49) close to MPZ Charcot-Marie-Tooth gene which is associated with AN

- Nystad M, Fagerheim T et al. Mutat Res 2008;637(1-2)56-65
Summary

- Auditory Neuropathy accounts for 8-10% congenital SNHL
- **Auditory Neuropathy does occur with cCMV**
- Axonal deafferentiation is one proposed mode of action
- In our study population 3 of (11%) had cCMV without other risk factors
- Guthrie card is only a helpful diagnostic tool if it is positive
- Auditory Neuropathy in cCMV can improve but also present late
- **Confirmation of Auditory Neuropathy changes audiological management**
- cCMV potentially infects the entire auditory pathway
- Auditory Neuropathy can be missed on a single assessment
Discussion

- Larger prospective cohorts saliva, urine, blood samples needed
- Our study will likely miss cases on Guthrie card retrospectively so be an underestimation
- Should audiology follow up in the first 1-2 years be ABR/ASSR/OAEs
- Are AN cases being missed because they fluctuate as do cochlear losses
- Does CMV damage development of cochlear nerve as it can the cochlear
- Do fluctuations and deteriorations result from different virus actions
- Premature infants are a distinct group who may require repeated CMV testing
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