Atypical Audiovestibular manifestation of connexin 26 variants

John Wong[1] BSc MSc, Laura Strachan[1] BSc, Javed Iqbal [2] BSc MSc
Prof Soumit Dasgupta[1] MBBS DLO MS FRCS MSc FIAOHNS FRCP

[1]Paediatric Audiology and Audiovestibular Medicine, Alder Hey Children's NHS Foundation Trust, Liverpool.
[2]Paediatric Audiology, East Lancashire NHS Trust.

Introduction

Connexin 26 accounts for up to 50% of cases of non-syndromic sensorineural hearing loss being the commonest genetic cause for hearing loss [1]. The majority are recessive. Hearing loss is heterogenous but is largely congenital and identified in new-born hearing screening (NHSP). Late onset/progressive hearing loss is a rare phenotype in a few rare sub genotypes. Up to 30% demonstrate late-onset hearing loss, starting in childhood [2].
Vestibular quantification is hardly reported in Connexin 26 mutations.

We present 2 case studies. Case 1 is Met34Thr variant and case 2 is p.Val37Ile variant both of which are rare (Chai Y, et al 2015). Pure Tone Audiometry, Tympanometry, Videonysatgmography (VNG) without optic fixation, Video head impulse test (vHIT), Suppression head impulse test (SHIMP) and Cervical vestibular evoked myogenic potential (cVEMPs) were performed with Alder Hey vestibular laboratory defined norms.

CASE 1

- A child failed a school hearing screening test. Subsequent testing PTA revealed a sensorineural hearing loss (see Figure 1).
- New-born hearing screening: Bilateral clear responses were obtained with AABR, with no clear responses using AOAE's
- Investigations
- Normal Neurological system examination.
- CT scan: Right posterior semi-circular canal dehiscence (see Figure 2).
- vHIT: Normal (see Figure 3). VEMP: Hypofunction on the left (see Figure 4)
- Confirmed Connexin 26 variant as cause of hearing loss Homozygous c.101T>C p.(Met34Thr) variant in exon 2 of the GJB2 gene.

Outcome

- Hearing aids subsequently fitted and there has been an improvement in his subjective attention and listening ability.

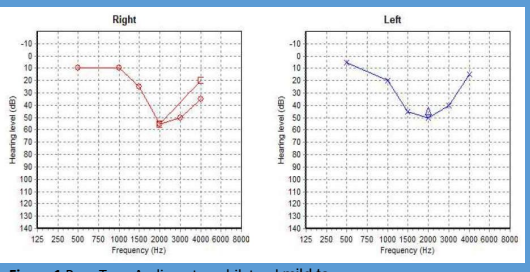

Figure 1 Pure Tone Audiometry – bilateral mild to moderate high frequency sensorineural hearing loss

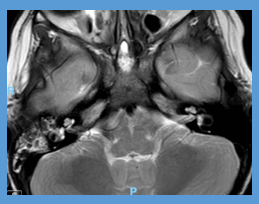

Figure 2 CT scan showing right posterior semi-circular canal dehiscence.

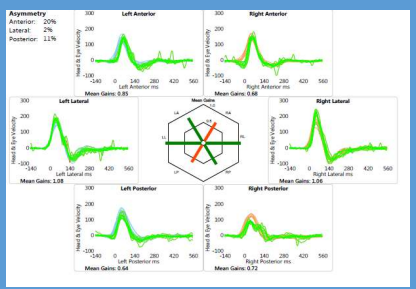

Figure 3 vHIT test was normal with good vestibulo-ocular reflex gain across the six semi-circular canals.

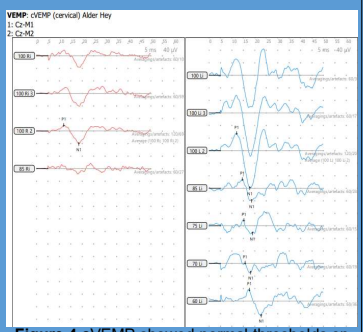

Figure 4 cVEMP showed normal thresholds on the right side. On the left side there were large amplitudes with lowering of thresholds to 60dB. There was asymmetry between ears at 26%.

CASE 2

- A child failed a school hearing screen. Subsequent testing: TEOAE absent PTA – (See Figure 5).
- History: Born at 35 weeks gestation. Three days of antibiotics including Gentamicin at birth following sepsis screen. No other risk factors for developing hearing loss. No clear responses on new-born hearing screening AOAE and AABR led to a referral. They had time on special care but didn't meet any of the criteria for specific risk factors. Click ABR at birth was satisfactory

Investigations

- Genetic testing confirmed variant c.109G>A (p.Val37Ile) homozygous.
- Vestibular test battery was satisfactory with vHIT and VEMPs (see Figure 6 & 7).

Outcome

- Hearing aids were fitted and upon their review there was a significant improvement in speech production. At present he is an extremely bright child excelling academically.

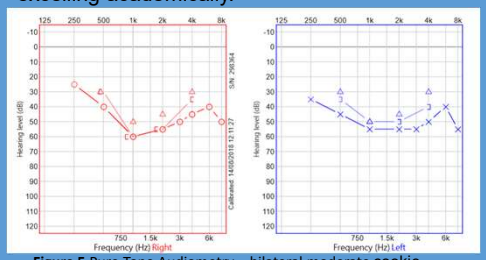

Figure 5 Pure Tone Audiometry – bilateral moderate cookie bite hearing loss.

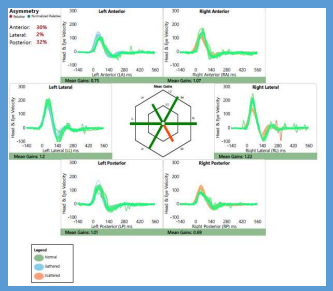

Figure 6 – vHIT Normal semicircular canal function

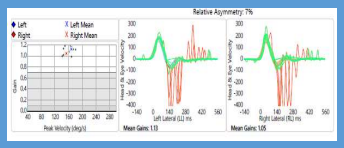

Figure 7 – Normal anticompensator saccades for SHIMP indicating good function of cerebellar clamp over VOR and peripheral function.

Discussion & Conclusion

- **These cases implicate the value of school hearing screening programmes to capture late onset, progressive hearing losses.**
- **M34Thr and p.VAL37Ile variants are pathogenic but have distinct features resulting in reduced penetrance.**
  - The M34Thr allele failed to co-segregate with hearing loss in several families, raising the possibility that M34T allele is a benign polymorphism.
  - It has been reported that Val37Ile homozygotes lose hearing at approximately 1 dB per year, suggesting an age-dependent penetrance of the hearing loss phenotype [4].
  - Val37Ile is also associated with sudden loss.
- **Vestibular dysfunction has not been widely recognized as a commonly associated clinical feature.**
  - To the authors knowledge saccular dysfunction through pathological cVEMPs has not been previously reported in the paediatric population. although the percentage of vestibular dysfunction is statistically higher in adults related to GjB2 mutation [3].

References
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