Atypical Audiovestibular manifestation of connexin 26 variants

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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.

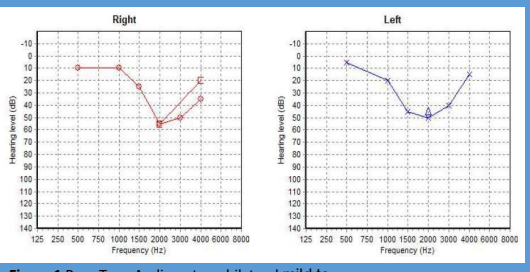

Figure 1 Pure Tone Audiometry – bilateral mild to moderate high frequency sensorineural hearing loss

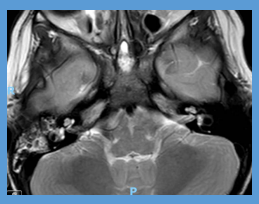

Figure 2 CT scan showing right posterior semi-circular canal dehiscence.

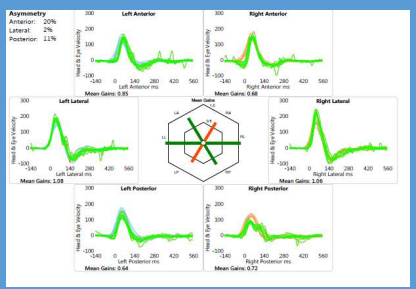

Figure 3 vHIT test was normal with good vestibulo-ocular reflex gain across the six semi-circular canals.

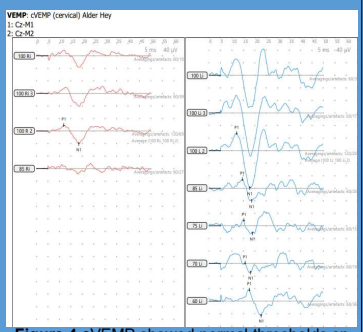

Figure 4 cVEMP showed normal thresholds on the right side. On the left side there were large amplitudes with lowering of thresholds to 60dB. There was asymmetry between ears at 26%.

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.

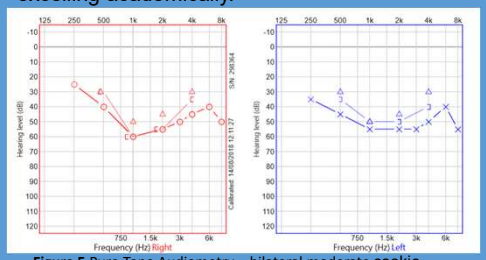

Figure 5 Pure Tone Audiometry – bilateral moderate cookie bite hearing loss.

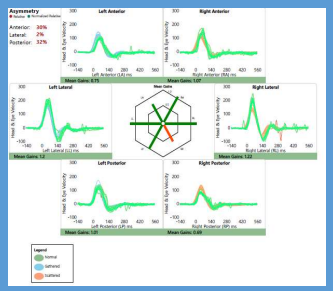

Figure 6 – vHIT Normal semicircular canal function

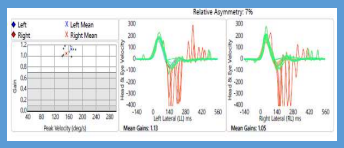

Figure 7 – Normal anticompensator saccades for SHIMP indicating good function of cerebellar clamp over VOR and peripheral function.

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
1. Zhu Y, Chen J, Liang C, Zong L, Chen J, Jones RO, Zhao HB. Connexin26 (GJB2) deficiency reduces active cochlear amplification leading to late-onset hearing loss. Neuroscience. 2015 Jan 22;284:719-729. doi: 10.1016/j.neuroscience.2014.10.061. Epub 2014 Nov 5. PMID: 25451287; PMCID: PMC4268423.
2. Todt I, Hennies HC, Basta D, Ernst A. Vestibular dysfunction of patients with mutations of Connexin 26. Neuroreport. 2005 Aug 1;16(11):1179-81
3. Kasai M, Hayashi C, Iizuka T, Inoshita A, Kamiya K, Okada H, Nakajima Y, Kaga K, Ikeda K. Vestibular function of patients with profound deafness related to GJB2 mutation. Acta Otolaryngol. 2010 Sep;130(9):990-5
4. Wu CC, Tsai CH, Hung CC, et al. Newborn genetic screening for hearing impairment: a population-based longitudinal study. Genetics in medicine : official journal of the American College of Medical Genetics. 2017;19(1):6-12

Advancing tinnitus research and researcher training: a case study review and future perspectives

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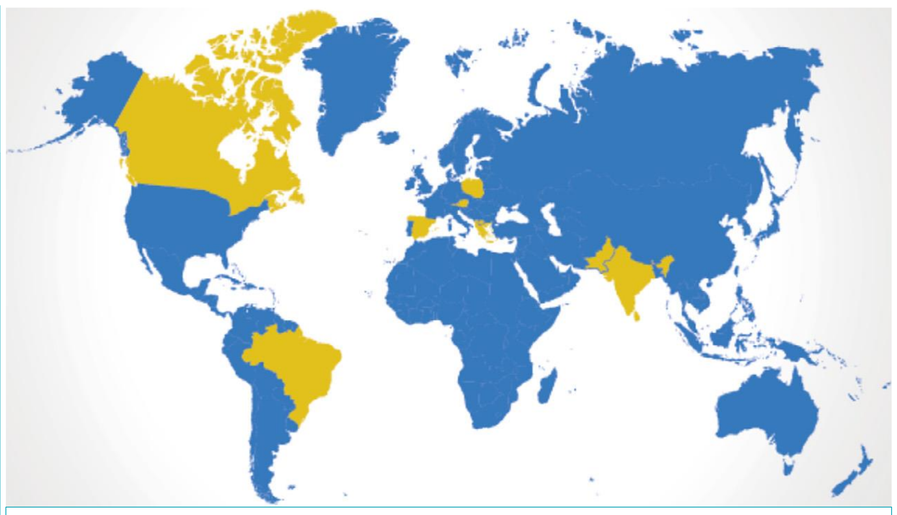
1. Background

Tinnitus affects around 1/10 people and can have a major impact on quality of life. More research is needed to address even the most fundamental questions, such as whether it is a symptom or a condition.

ESIT (European School on Interdisciplinary Tinnitus) was a step in the right direction: an EU-funded DTP (Doctoral Training Partnership) comprising clinicians, academics, commercial partners, patient organisations, and public health experts from various European countries, with students from across the world.

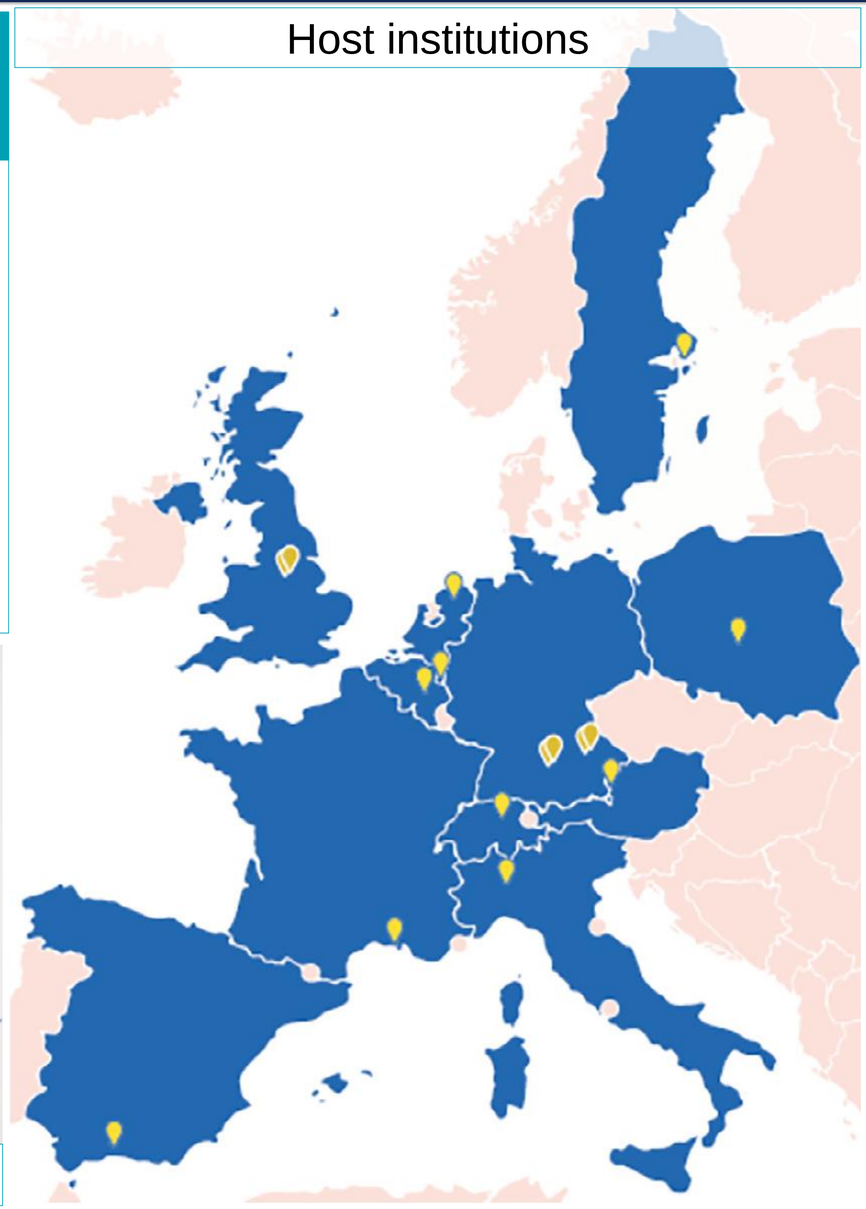
2. How ESIT Worked

An interdisciplinary and intersectoral DTP, it offered network-wide training, integrating academic, clinical and industry partners and benefactors, where individual PhD projects interconnected and novel.



Origin countries of students

Host institutions



3. Results

- Social/networking interaction at Training Schools and conferences was considered most valuable
  - 7 non-ESIT students attended these in total
- Clinical internships provided real-world experience to direct potential impact of research
- Secondments were important: they were collaborative and provided varied perspectives
- International nature of the DTP highlighted language/culture differences, visa issues, even technology problems
- Up to April 2020: 21 peer-reviewed publications, of which 18 student-led, plus student representation at multiple international conferences, including as invited speakers

'The experience highlighted how important it is to engage with patients: they benefit from having a scientist willing to talk to them and to acknowledge their condition, and scientists can generate more meaningful research questions based on patients' suggestions, experiences, stories.'

4. Conclusions

- Community is paramount to PhD journeys
- PPI groups should be involved at all stages of research to ensure relevance
- Tinnitus research needs more time, money and input
- Health and wellbeing, and a dedicated support system, must be included in international programmes

nottingham.ac.uk/research/groups/hearingsciences

esit.tinnitusresearch.net/