Neurotransmitter and Neurotransmitter Receptor Expression in the Human Saccule and Vestibular (Scarpa’s) Ganglion

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Introduction: Little is known about neurotransmission in the vestibular system, especially in humans. Knowledge is key to understand vestibular function and to identify potential molecules for pharmacological treatment. In addition, human data is pivotal to translation of experimental findings into humans.

Objectives: We assessed neurotransmitter and neurotransmitter receptor expression in the human saccule and vestibular ganglion using immunohistochemistry.

Methods: Tissue from the human saccule and vestibular ganglion was sampled during vestibular schwannoma surgery. Immunohistochemistry was performed for a series of neurotransmitters and receptors including L-glutamate, glutamate receptor 1 (GluR1), metabotropic glutamate receptor (mGluR), cholecystokinin, cholecystokinin receptor A (CCKAR) and B (CCKBR), serotonin, serotonin receptor 1D (5-HT1D), dopamine, dopamine transporter (DAT), dopamine receptor 2 and 5, histamine receptor 1 and 3 (H1R), GABA, GABA A receptor alpha (GABAαRα) and B receptor 2 (GABAβR2).

Results: In the human saccule, the neuroepithelium expressed CCKBR, GABAαRα, GABAβR2, GluR1 and mGluR. The epithelial lining expressed CCKAR, DAT, GluR1, mGluR and H3R, and the subepithelial stroma expressed CCKBR, dopamine, GABAαRα, GluR1, L-glutamate and 5-HT1D. The human vestibular ganglion cells expressed CCKBR, dopamine, GABAαRα, GABAβR2, GluR1 and mGluR, the related nerve fibers expressed L-glutamate, mGluR and 5-HT1D, and the supporting cells and stroma expressed CCKBR and 5-HT1D.

Conclusions: This study provides a comprehensive overview of the neurotransmitters and receptors expressed in the human saccule and vestibular ganglion. These neurotransmitters and receptors might play a role in peripheral neuronal signaling and signal modulation. Furthermore, these findings indicate that pharmacological effects on vestibular function could also have a peripheral origin.

Disclosure of Interest: None Declared

Keywords: immunohistochemistry, neurotransmitter, saccule, vestibular system
**Short Papers**

*Neuro Otology*

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**Enlarged Vestibular Aqueduct: Disease Characterisation and Exploration of Potential Clinical Predictors for Cochlear Implantation.**

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**Introduction:** Hearing loss (HL) associated with Enlarged Vestibular Aqueduct (EVA) is markedly heterogenous, with phenotypes ranging from the identification of profound deafness in infancy to young children and adolescents with relatively stable HL without the need for cochlear implantation (CI) 1,2. Current management is reactive, seeking to identify early any deterioration in hearing or detrimental effects upon child development. Therefore, there is an unmet need to improve our understanding of the natural history of EVA by exploring potential clinical predictors (prognostic factors) for HL severity and progression. This will enable CI clinicians to optimise their approaches to CI candidacy selection and timing of surgery.

**Objectives:** The objectives of this study are to provide a detailed case characterisation of the largest European cohort of EVA patients to date and explore the relationship between candidate prognostic factors and timing of CI surgery.

**Methods:** The design of this study aimed to meet recognised standards for robust prognostic factor research 3. We undertook a retrospective review of 150 patients with confirmed radiological diagnosis of EVA, across three UK CI centres, between January 1995 to January review 2021. Data acquisition focussed on demographics, genotype, longitudinal audiological data and radiological findings. Main outcome measures were age at which audiological candidacy for CI was met and age at 1st CI surgery. Statistically significant associations between candidate prognostic factors and the outcome measures were further explored with multivariate analysis.
Results: EVA was predominately a bilateral condition (144/150) with increased prevalence in females (M:F, 64:86). 51.7% of patients failed newborn hearing screening, with 65.7% having HL diagnosed by 1 year. Moderate to severe and severe to profound HL were reported most frequently at earliest audiological testing. In 123 patients, median age that audiological candidacy for CI was met for at least one ear was 2.75 years. Median age at first CI was 5 years (140/150) and 57.6% of patients were ultimately bilaterally implanted. Incomplete partition type 2 was present in 63/140 patients. Pendred syndrome, ethnicity and presence of incomplete partition were not significantly associated with earlier CI surgery. There was an association for male patients to be assessed earlier for CI, and to have first CI surgery earlier than females (See table 1). These associations were further explored with multivariate linear regression, demonstrating that male patients have first CI assessment and first CI surgery significantly earlier than females (coefficient of male gender in the linear regression for log(Age first seen for CI assessment)=-0.58, 95% CI (-1.03,-0.13), p-value=0.012, coefficient of male gender in the linear regression for log(age at first CI surgery)=-0.43, 95% CI (-0.82,-0.05), p-value=0.028).

Conclusions: Currently this is the largest European cohort to characterise EVA patients. It therefore provides useful clinical information regarding broad timeframes for CI surgery when counselling newly diagnosed patients with EVA. We provide evidence that EVA patients should be closely monitored for CI candidacy, especially within the first 3 years of life. Our exploratory prognostic factor study design builds confidence that male gender is an independent prognostic factor for earlier timing and assessment for CI surgery in EVA patients.


**Disclosure of Interest**: None Declared

**Keywords**: Enlarged Vestibular Aqueduct, Hearing Loss, Prognosis
Genotype-phenotype correlations of pathogenic COCH variants in DFNA9: a HuGE systematic review and audiometric meta-analysis

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Introduction: Pathogenic missense variants in COCH are associated with DFNA9, an autosomal dominantly inherited type of progressive sensorineural hearing loss with or without vestibular dysfunction.

Objectives: This study presents a systematic review and meta-analysis of all known DFNA9-associated COCH variants and their associated phenotypes.

Methods: HuGENet guidelines were applied in this systematic review. The literature search yielded 48 studies describing the audiovestibular phenotypes of 27 DFNA9-associated variants in COCH. A meta-analysis of audiometric data was performed by constructing age-related typical audiograms and by performing analyses on the age of onset and progression of hearing loss.

Results: A detailed overview of genotype-phenotype correlations of all currently known pathogenic COCH variants associated with DFNA9 is presented. Significant differences were found between the calculated ages of onset and progression of the audiovestibular phenotypes of subjects with pathogenic variants affecting either the LCCL domain of cochlin, or the vWFA2 and Ivd1 domains.

Conclusions: The audiovestibular phenotypes associated with DFNA9 are highly variable. Variants affecting the LCCL domain of cochlin generally lead to more progression of hearing loss when compared to variants affecting the other domains. This review serves as a reference for prospective natural history studies in preparation of future therapeutic interventions.

Disclosure of Interest: None Declared

Keywords: COCH, DFNA9, SNHL, vestibulocochlear dysfunction


Introduction: DFNA9 is characterized by adult-onset progressive sensorineural hearing loss (SNHL) and vestibular impairment. The last decade was marked by the emergence of new clinical diagnostic tools, such as the video Head Impulse Test (vHIT) and Vestibular-Evoked Myogenic Evoked Potentials (VEMPs), expanding our evaluation to all six SCC and the otolith organs.

Objectives: The aim of this study was to determine milestone ages (start and maximal hearing deterioration, potential eligibility for hearing aids and cochlear implants based on pure tone average (PTA)). Age-Related Typical Audiograms (ARTA) were constructed. The authors also aimed to determine which labyrinthine part shows the first signs of deterioration and which SCC function declines at first and to determine the age of reaching vestibular areflexia.

Methods: 111 Belgian and Dutch p.P51S variant carriers were enrolled for audiological and vestibular investigation. The milestones ages were derived from non-linear regression model of hearing thresholds against age, interaural right-left asymmetry was assessed and ARTAs were built. The following vestibular function tests were applied in two different centers: ENG/VNG, vHIT and VEMPs. The age of onset of vestibular dysfunction was determined both with categorical and numeric approach. The same method was applied for determining the age at which vestibular function declined beyond the limits of bilateral vestibulopathy (BVP).

Results: Hearing dysfunction in p.P51S carriers already start in the 3rd decade. Predictions (ARTA) did not show any gender-effect. At about 48-50 years of age on average, the majority of DFNA9 patients need conventional hearing aids, whereas this is about 56-59 years for cochlear implants. There is a high degree of individual interaural asymmetry and inter-individual variability throughout all ages. Otolith function was declining first (3rd decade), followed by caloric response (5th decade) and vHIT VOR-gains (5th – 6th decade). BVP on caloric response was estimated at 53 years of age and between 78 and 85 years of age for the three SCC on vHIT tests. Loss of C-VEMP response was estimated at about 46 years of age.

Conclusions: This study demonstrates that the onset of sensorineural hearing deterioration starts in the 3rd decade and probably even earlier. DFNA9 expresses similarly in male and female carriers, but male carriers are much more difficult to identify in early stages of the disease. Former hypothesis of vestibular decline preceding hearing deterioration by 9 years was not confirmed for hearing loss at high frequencies, which tended to start earlier. There is a typical vestibular
deterioration hierarchy. Comprehensive assessment of the natural course of DFNA9 is of particular interest to predict the age of onset which will help to design studies in the search for disease-modifying therapies.

Disclosure of Interest: None Declared

Keywords: SNHL, cochlear hereditary hearing loss, DFNA9, COCH, Age-Related Typical Audiograms (ARTA), bilateral vestibulopathy – vestibulo-ocular reflex – sensorineural hearing loss – progressive vestibulocochlear dysfunction – human COCH protein
The Healthy Hearing Ears Initiative – Investigating healthcare consumption in patients with chronic otitis media related hearing loss

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Introduction: Chronic otitis media and the associated hearing loss is a global health concern that places significant burden on patients and healthcare systems.

Objectives: To gain a better understanding of resource utilisation and costs related to chronic otitis media.

Methods: We conducted a registry study to map healthcare utilized by individuals with the disease in western Sweden. Cost analyses were also performed to determine key drivers of healthcare expenditure.

Results: Data covering 656 adult subjects with chronic otitis media that underwent a middle ear surgery between 2014 and 2018 were extracted from the Swedish National Patient Register, including healthcare contacts related to all publicly funded specialist ENT-care, audiological care and primary care for disease of the ear and mastoid process. Data show that these subjects made 13,783 health care contacts at a total cost of 60 million EUR between 2014 and 2018. The mean cost per subject was 9.177 EUR, ranging between 391 to 46.184 EUR per individual. In the most expensive quartile, the average cost per individual was 18.978 EUR over the five-year period and 60% of total costs were associated with inpatient ENT-care.

Conclusions: Chronic otitis media and its sequelae are associated with high ENT resource utilisation that does not diminish after surgical intervention, which places a long-term burden on healthcare systems. A significant portion of costs were attributed to revision middle ear surgeries, indicating that some patients could be managed more effectively.

Disclosure of Interest: M. Hol Conflict with: Financial support to the authors' institution for conducting clinical studies from Cochlear

Keywords: chronic otitis media, health economics, healthcare utilization, hearing loss
The role of a novel contrast-enhanced microCT method for ex vivo CI insertion trauma studies

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Introduction: Background: A cochlear implant (CI) is a medical prosthesis that restores auditory perception in individuals, suffering from severe perceptive hearing loss. An important risk of CI surgery remains electrode insertion trauma, which occurs in up to 40% of insertions¹ and can have a negative impact on the hearing outcome, especially in the increasing population of CI-patients with residual hearing. The mechanisms of insertion trauma and preventive strategies are intensively being studied in human temporal bones and models²³.

Objectives: To study cochlear implant insertion trauma, therefore we need to develop a commonly available, non-destructive method for reliable insertion trauma evaluation. In addition to create scalable models, representative for the cochlear variant anatomy, to enable controlled, repeatable insertion experiments.

Methods: We have implemented and standardized contrast-enhanced microCT imaging (CE-μCT) for the evaluation of in total seven fresh-frozen human cadaveric cochleae. Hafnium-substituted Wells-Dawson polyoxometalate (Hf-POM) was used as a non-invasive contrast-enhancing staining agent (CESA)⁴, and its diffusion time throughout the cochlea was assessed. The CE-μCT results were validated by comparison to histological images. In four of these cochleae, trauma was induced after the first imaging, followed by generation of new CE-μCT datasets. μCT images of two cochleae were used to produce 3D printed models of the scala tympani. Their anatomical accuracy was quantified as the geometric deviation of the printed 3D model from the original cochlea, expressed as the Root Mean Square Error (RMSE). Saline and soap solution were tested to model the intracochlear fluid for insertion mechanics. The mechanical accuracy of the models was assessed by evaluating if full electrode insertion was possible and by measuring the forces during slow insertion of a straight electrode into the models versus 4 fresh-frozen cadaveric cochleae.

Results: CE-μCT allowed visualizing not only the mineralized, but also the soft tissues within the cochlea. Sufficient CESA absorption in the intracochlear soft tissues was systematically achieved after 72h of submersion in the staining solution. CE-μCT also enabled reliable evaluation of cochlear damage in accordance with insertion trauma classification by Eshraghi et al.⁵ The anatomical accuracy of 3D printed scala tympani models was within the limits of cochlear anatomical variability⁵ with RMSE ≤ 0.11mm. Soap solution was determined to be a better model for intracochlear fluid, as it allowed for full electrode insertion, which could never be achieved with the saline solution. The maximum insertion forces were comparable for full electrode insertion in 3D models (median; IQR = 86.84mN; 38.36mN) and in fresh-frozen cochleae (median; IQR = 106.08mN; 71.72mN).
**Conclusions:** Our study reports on CE-μCT imaging as a novel non-invasive imaging method for the evaluation of fresh human cochleae. On the one hand, it enables detailed, quantitative 3D assessment of electrode insertion trauma, which is crucial to detect damage and unequivocally superior to a limited number of histological 2D sections. As CE-μCT is a non-destructive method, false positive results for insertion trauma are unlikely and histology remains possible after imaging. On the other hand, CE-μCT images are a reliable base for development of anatomically and mechanically accurate, scalable cochlear models.

**References:**

**Disclosure of Interest:** N. Verhaert Conflict with: Research Foundation Flanders, Belgium, A. Starovoyt Conflict with: Research Foundation Flanders, Belgium, G. Pyka: None Declared, E. Shaheen: None Declared, T. Putzeys Conflict with: Research Foundation Flanders, Belgium, C. Politis: None Declared, J. Wouters: None Declared, G. Kerckhofs: None Declared

**Keywords:** cochlear implantation, Insertion trauma, Radiology
Autonomous inner ear access in Robot Assisted Cochlear Implant Surgery (RACIS)

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Introduction: The HEARO® robotic system is an assistive otological next generation surgical robot to assist the surgeon with cochlear implantation (CI) surgery. It provides software-defined spatial boundaries for orientation and reference information to anatomical structures in order to execute drilling directly towards inner ear to facilitate a keyhole access.

Objectives: Here, we report the feasibility but also safety and efficiency of this procedure for Robot assisted cochlear implant surgery (RACIS) in the first 25 patients.

Methods: All patients indicated for cochlear implantation in a routine conventional work-up fulfilling the audiological criteria were radiologically screened. Patients with suitable anatomy were approached for participation with written informed consent. This clinical trial was approved by the medical ethics comity.

Results: Seven cases had not passed the radiological screening and only one patient opted to have conventional CI surgery. The RACIS was performed in 25 patients including 6 women (24%) and 19 men (76%). The age values of 25 patients ranged from 20 to 89 (Figure 5). Three procedures were converted to conventional surgery because of our safety protocols: mainly for the facial nerve during drilling of middle ear access. In total 22 procedures were successfully drilled up to the level of inner ear without any facial nerve injuries or any other adverse events. From these 22 cases all patients had a full insertion of the cochlear implant. In 1 case the post op image showed that the last electrode was at the level of the round window. Although the patient had auditory sensations with this electrode, it was the only electrode that was switched off by the audiologist. Specific cases with aberrant anatomy, surgical challenges and anatomical accuracy will be discussed in the presentation.

Conclusions: We conclude that the HEARO procedure is safe and effective assistive tool for a cochlear implant surgeon.

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A New Pathogenic Variant in POU3F4 Causing Deafness Due to an Incomplete Partition of the Cochlea Paved the Way for Innovative Surgery.

Prediction of the Cochlear Implant Electrode Insertion Depth: Clinical Applicability of two Analytical Cochlear Models.
Comparison of the Surgical Techniques and Robotic Techniques for Cochlear Implantation in Terms of the Trajectories Toward the Inner Ear.

Topsakal V, Matulic M, Assadi MZ, Mertens G, Rompaey VV, Van de Heyning P.

Disclosure of Interest: None Declared

Keywords: Sensorineural hearing loss, Cochlear implantation, Robotic surgery, Image guided surgery
How cochlear implant intraoperative electrophysiological measurements correlate with each other and with inner ear dimensions?

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Introduction: A limiting factor of cochlear implant technology is the spread of electrode-generated intracochlear electrical field (EF) leading to spread of neural excitation (SOE). However, the exact correlation between these two is unknown. Earlier studies have found that electrically-evoked compound action potentials (eCAP) thresholds are affected by the distance between electrode contact and modiolus, diameter of the bony cochlear nerve canal (BCNC) and size of the cochlear nerve (CN). However, detailed characterization of the effect of inner ear dimensions on eCAP thresholds is missing.

Objectives: To investigate the relation of the spread of the intracochlear EF, assessed via transimpedance matrix (TIM), and SOE. To evaluate the effect of cochlea diameter on TIM and SOE. To assess the relationship between inner-ear dimensions and eCAP thresholds.

Methods: For the TIM and SOE comparison, a total of 43 consecutive patients (ages 0.7–82 years; 31.0 ± 25.7 years, mean ± SD) implanted with a Cochlear Nucleus CI522 or CI622 cochlear implant (altogether 51 ears) were included in the study. For the inner-ear dimension and eCAP threshold measurements, 52 pediatric patients with congenital severe hearing loss (27 females and 25 males; ages 0.7–2.0 years; 1.0 ± 0.3 years, mean ± SD) consecutively implanted bilaterally with Cochlear Nucleus CI422, CI522, or CI622 implants were included. All the patients were implanted with lateral-wall Slim Straight electrode arrays. For TIM and SOE measurements, the stimulated electrodes were in the basal, middle, and apical parts of the electrode array. The eCAP thresholds were recorded from all electrodes. The anatomical structures of the inner ear were measured from preoperative CT and MRI scans.

Results: Approximately 90% of the individual TIM and SOE profiles correlated with each other (p < 0.05; r = 0.61–0.99). Also, the widths of the TIM and SOE peaks, computed at 50% of the maximum height, exhibited a weak correlation (r = 0.39, p = 0.007). The 50% widths of TIM and SOE were the same only in the apical part of the electrode array; in the basal part SOE was wider than TIM, and in the middle part TIM was wider than SOE (p < 0.01 and p = 0.048, respectively). Within each measurement, TIM 50% widths were different between all three parts of the electrode array, while for SOE, only the basal electrode differed from the middle electrode. The size of the cochlea and the 50% widths of TIM and SOE had the strongest correlation in the middle part of the electrode array (r = −0.63, and −0.37, respectively). For eCAP thresholds, a correlation between electrode insertion angle and eCAP threshold was found (p < 0.001). Also, eCAP thresholds were affected by cochlea size (p < 0.001). There was a correlation between cochlea and BCNC diameters (r = 0.39, p < 0.001).
Conclusions: A correlation between the spread of intracochlear EF and neural SOE was found at least in the apical part of the electrode array. Large cochleae are associated with more focused TIM and SOE. Electrode insertion angle and cochlea size affect eCAP thresholds.

Disclosure of Interest: None Declared

Keywords: cochlear implantation, electrophysiological measurement, inner ear anatomy
**Auditory Implants - Clinical Science**

**EAONO21-OR-010**

**Long-term follow-up of a wide diameter bone anchored hearing implant: the 10-year experience on stability, survival and tolerability of an implant loaded at 3 weeks after surgery.**

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**Introduction:** Hearing rehabilitation through direct bone conduction is a well-established method to overcome bilateral conductive and mixed hearing loss, as well as unilateral conductive hearing loss and single-sided deafness. The original auditory osseointegrated implant was a titanium implant with an as-machined surface, designed by Brånemark. Later, it became commercially available as the Cochlear™ Baha® flange fixture. In 2009, Cochlear™ introduced the BIA300®. Dun et al. and Nelissen et al. reported the 6-month and 3-year results from a multicentre, randomized controlled trial of the BIA300® implant. Subsequently, den Besten et al. reported the 5 year results. Based on the favorable outcomes of these studies, it was thought that the time between implantation and sound processor loading could be shortened. To investigate this further, a prospective controlled trial on loading the BIA300® implant 3 weeks post-surgery was performed. The outcomes of this group were compared with the outcomes of patients that were implanted with the same implant but were loaded 6 weeks post-surgery. After 3 years of follow-up the authors concluded that loading the BIA300® implant 3 weeks post-surgery was safe in adult patients with normal bone-quality. To go even further, previous research suggested that wide diameter implants can be safely loaded 2 weeks post-surgery, 1 week post-surgery, and extremem: 1 day after surgery. However, these last-mentioned studies only followed up for a maximum period of 1 year, which means longer-term data on extremely reduced loading-times are still unavailable.

**Objectives:** To compare stability, survival and soft tissue reactions between a wide diameter (test) and a previous generation (control) bone anchored hearing implant, and to ascertain the safety of loading the test implant 3 weeks post-surgery, at a 10-year follow-up.

**Methods:** This study is a continuation of three previously completed, multicentre, randomized, controlled trials and consisted of 1-2 follow-up visits till 10 years after implantation. Fifty-one of the 72 participants from the previous trials were included. These patients either received a test or control implant and were either loaded 3 or ≥6 weeks post-surgery.

**Results:** The test implant showed significantly higher implant stability quotient (ISQ) values compared with the control implant throughout the entire 10-year follow-up. For both implants, the mean ISQ high at 10 years was higher compared with the first follow-up visit. No significant differences in change of ISQ high from baseline to 10 years were noticed between both implant and loading groups. Soft tissue reactions were scarcely found. At the 10-year follow-up visit, no patients presented with Holgers ≥2. Excluding explantations, the implant survival rate was 100.0% and 78.6% for the test implant group and control implant group respectively, and 93.3% for the 3-week loading group.
Conclusions: The test implant showed superiority in terms of higher mean ISQ values and implant survival during the entire 10-year follow-up. In addition, loading the test implant at 3 weeks post-surgery is safe, based on the current study, as long-term results show high ISQ values and good implant survival.

References:
Short Papers


Disclosure of Interest: E. Teunissen Conflict with: Cochlear Bone Anchored Solutions & Oticon Medical, C. Caspers Conflict with: Cochlear Bone Anchored Solutions & Oticon Medical, M. Vijverberg Conflict with: Cochlear Bone Anchored Solutions & Oticon Medical, E. Mylanus Conflict with: Cochlear Bone Anchored Solutions & Oticon Medical, M. Hol Conflict with: Cochlear Bone Anchored Solutions & Oticon Medical, Conflict with: Cochlear Bone Anchored Solutions & Oticon Medical

Keywords: bone conduction implants
Introduction: When a vestibular schwannoma arises from a nerve sheath within the bony labyrinth, it results in an intralabyrinthine schwannoma (ILS). Simultaneous tumor removal and hearing rehabilitation by inserting a cochlear implant into the cochlea has become a beneficial option for patients. Follow-up with regard to tumor growth is more complicated in this situation. Therefore, the question arises of what structures are involved in the extension of ILS, as this may help to estimate the risk of continued growth.

Objectives: The aim of this study is to perform a histopathologic analysis of temporal bones with an ILS in order to characterize its extension.

Methods: Archival temporal bones with a diagnosis of sporadic schwannoma were identified. Both symptomatic and occult non-operated ILS were included for further analysis. Sections of each case were examined to determine the origin of the tumor, its precise location in the labyrinth, and its extension.

Results: A total of 6 ILS were identified, with four intracochlear and two intravestibular schwannomas. All intracochlear schwannomas involved the osseous spiral lamina with two extending into the modiolus. The intravestibular schwannomas were limited to the vestibule, but growth into the bone next to the crista of the lateral semicircular canal was observed in one patient.

Conclusions: Complete removal of an ILS may require partial removal of the modiolus or bone surrounding the crista ampullaris as an ILS may extent into these structures, risking damage of the neuronal structures. Due to the slow growth of the ILS, it remains unclear if a complete resection is required with the risk of destroying neural structures hindering hearing rehabilitation with a cochlear implant.

Disclosure of Interest: None Declared

Keywords: Histopathology, vestibular schwannoma
Round Window Membrane Obstructions and their Possible Effect on Intratympanic Therapy

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Introduction: Recent advances in the understanding of aetiologies of inner ear dysfunction has enabled the identification of molecular pathways, enabling the identification of therapeutic agents targeting the inner ear1. However, the unique location of the inner ear poses delivery challenges due to its protected position within the otic capsule and its epithelial barriers. The intratympanic approach of drug delivery has gained popularity, bypassing the blood-perilymph barrier and toxicity and side effects associated with systemic administration1-3. A variety of intratympanic delivery strategies exist, ranging from tympanic membrane injections to implantable pump systems. However multiple factors affect drug distribution within the perilymph compartment including molecular size, liposolubility and the presence of round window membrane (RWM) obstructions4-7.

Objectives: The objective was to study the presence of RWM obstructions and to quantify their prevalence in a prospective study.

Methods: A prospective case study of patients receiving Otological surgery was carried out. Inclusion criteria were patients receiving surgery in whom the RWM could be adequately visualised either through a microscope or endoscope. Exclusion criteria were patients in whom an accurate assessment of the RW niche or membrane could not be made due to inadequate exposure or view. A literature review on the topic was conducted.

Results: Sixty-five (61.9%) out of 105 ears had an obstructed RWM, the majority of which were extraneous RWMs or fibrous tissue.
Conclusions: Studies on RWM obstructions are limited. As far as the authors are aware, this is the third and largest intraoperative clinical study in the literature. Silverstein et al. conducted a retrospective chart review on 41 patients undergoing laser-assisted tympanostomy and middle ear endoscopy. They found 12 out of the 41 cases to have complete RWM obstructions with 7 having partial obstructions and 5 having complete obstructions, which gives a rate of 29% obstructed. Plontke et al. assessed RWM obstructions and removed them as part of their study on the surgical technique microcatheter implantation for drug delivery to the inner ear. They found the presence of extraneous RWM or fibrous plugs in 5 out of 25 cases (20%). Lastly, the most referenced study on RWM obstructions is a temporal bone study by Alzamil and Linthicum conducted in the House Ear Institute temporal bone laboratory. Out of 202 temporal bones, they found a RWM obstruction rate of 33%. Our study has a much different RWM obstruction rate compared to these aforementioned studies. One reason may be the higher proportion of paediatric patients in our cohort. This is the largest in vivo study on RWM obstructions. One reason for the individual variation in the therapeutic success of intratympanic drugs becomes evident when examining the RW niche. The passage of molecules can be hindered by the presence of an additional physical barrier, which we have found to occur in 61.9% of ears.


Disclosure of Interest: None Declared

Keywords: round window anatomy
Oto-endoscopy as a means to identify cholesteatoma remnants during cholesteatoma surgery.

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Introduction: Cholesteatoma surgery is very challenging, certainly with respect the retrotympanum.

Objectives: In this retrospective study, we aim to evaluate oto-endoscopy as a means of identifying cholesteatoma remnants after surgical excision of cholesteatomas under otomicroscopy, and the subsequent incidence of the development of residual cholesteatomas over the period of clinical follow-up.

Methods: Retrospective analysis of consecutively treated patients in the academic centre of the University Hospitals of Leuven, Belgium. The Supervisory Committee on Medical ethics of Leuven University has acknowledged this retrospective study as scientifically relevant and in line with prevailing ethical standards, as confined in the declaration of Helsinki (MP017279).

Between January 2012 and December 2020, 94 patients (58 male, 36 females, with a mean age of 29) were selected from our database by retrospective charge review. They were either operated for primary acquired cholesteatoma, recurrent acquired cholesteatoma or retracted tympanic membrane. All were operated using a canal wall up tympanoplasty (CWU) or an exclusively transcanal technique under the otomicroscope, with subsequent oto-endoscopic control for cholesteatoma remnants after apparent total removal of cholesteatoma. No hybrid, fully endoscopic nor fully microscopic cases were included. Furthermore, we evaluated the subsequent incidence of residual cholesteatomas over the period of clinical and MRI follow-up. Data were collected using medical records. Statistical analysis was performed using SPSS.

Results: Upon endoscopic evaluation after apparent total removal of cholesteatoma under the otomicroscope, we encountered intraoperative cholesteatoma remnants in 26 patients (27,66%). In 10 cases these remnants were seen in the antrum during an upfront exclusively transcanal approach, which necessitated an additional mastoidectomy and a conversion to a canal wall up mastotympanoplasty. The sinus tympani was the second most common site to find intraoperative remnants (n=8).

During the postoperative period of clinical and MRI follow-up, in 11 patients (11,70%) residual cholesteatoma was still detected. Of these patients 7 had a negative endoscopic control after otomicroscopic removal of cholesteatoma, and 4 had a positive endoscopic control. Further statistical analyses are ongoing.

Conclusions: Oto-endoscopy can be seen as a means to identify cholesteatoma remnants after otomicroscopic cholesteatoma surgery. Adding the oto-endoscope in cholesteatoma surgery during a canal wall up tympanoplasty (CWU) or an exclusively transcanal approach reduces the rate of postoperative residual cholesteatoma to the range seen after canal wall down tympanoplasty. Recently, full endoscopic and hybrid techniques have been adopted.
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**Keywords:** Cholesteatoma, oto-endoscopy, surgical technique
Functional ear symptoms referred to otology clinic: a new experience-driven clinical model

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Introduction: Functional otological symptoms include tinnitus, imbalance, otalgia and aural fullness in the absence of active ear disease. They occur due to complex changes in neurocircuitry involving limbic and sensory systems. The burden of functional disorders on otology clinic is yet to be quantified.

Objectives: To review the incidence and comorbidity of functional ear symptoms in new referrals to an adult otology clinic and present a clinical model based on neuroscientific concepts.

Methods: 1000 consecutive new referrals to adult otology clinic were retrospectively reviewed. In addition to primary diagnosis, functional ear symptoms were reviewed for incidence, age, sex, and underlying comorbidity.

Results: Functional disorder was the primary diagnosis in 346 patients (34.6%), occurring more commonly in females (60%). Of 346 patients, functional ear symptoms included tinnitus (69.1%), imbalance (23.7%), otalgia (22.8%), and aural fullness (19.1%), with more than one symptom occurring in 25.4%. Underlying conditions included sensorineural hearing loss (39%), emotional stress (30%), chronic illness (22%), chronic pain disorder (16%), anxiety and depression (8.7%), surgery (6.4%), noise induced hearing loss (4.6%), trauma (4.3%), migraine (3.2%), and fibromyalgia (2.3%).

Conclusions: Functional disorders commonly present to otology clinic (34.6% referrals), often in the presence of emotional stress or chronic illness. The brain has evolved for survival. Experiences adapt brain circuit activity based on development, adverse events, chronic illness, fear learning and memory, and emotional state. Stress sensitivity, aberrant salience, thalamocortical dysrhythmia, frontostriatal system impairment, central sensitisation, prediction error and somatosensory amplification are well documented concepts in a diverse range of functional disorders. We present a brain-centred clinical model for functional ear symptoms based on these concepts and our clinical experience. A basic understanding of these principles will significantly aid the otologist, neurotologist and other clinicians in managing patients with functional ear symptoms.

Disclosure of Interest: None Declared

Keywords: Functional, tinnitus, Vertigo
Impact of hearing disability and ear discharge on quality-of-life in patients with chronic otitis media: data from the multinational collaborative COMQ-12 study


Introduction: Chronic otitis media (COM) is a leading cause of acquired hearing impairment, particularly in the first five years of life and in developing countries, with an estimated global incidence of 4.76%. There are several disease-specific instruments used to assess patient health-related quality-of-life (HRQoL), capturing the overall burden of disease.

Objectives: This study aimed to assess how two disease-related factors, hearing disability and ear discharge, affect HRQoL in patients with COM.

Study Design: Multinational prospective cohort study.

Setting: Nine otology referral centers in eight countries

Patients: Adult patients suffering from COM.

Main Outcome Measure(s): Hearing disability and ear discharge was assessed by audiometry (DHSS formula) and otoscopy, respectively. Participants completed a native version of the Chronic Otitis Media Questionnaire-12 (COMQ-12). We determined how the two disease-related factors affect HRQoL by performing two separate analyses: (1) using a 6-item score combining responses to COMQ-12 items independent of hearing loss and ear discharge, and (2) using item 12 alone as a proxy for global HRQoL.

Results: This study included 478 participants suffering from COM. There was a significant association between HRQoL and hearing disability in the adjusted analysis. For every unit increase in the DHSS average hearing threshold, (1) there was an increase of 0.06 (95% CI [0.007, 0.121], p=0.0282) in the 6-item score, and (2) the adjusted odds of having a higher item 12 score was 1.03 (95% CI [1.01, 1.04], p=0.0004). There was no association between the presence of ear discharge and HRQoL in both COMQ-12 score analyses.
Conclusions: Knowledge of disease-related factors that influence HRQoL will aid interpretation of patient-reported measures for COM. Patients with a greater degree of hearing impairment appear to have poorer HRQoL, which is not exacerbated by the presence of ear discharge. The magnitude of post-operative hearing improvement rather than the attainment of a dry ear may be a better indicator of surgical success from the patient’s perspective.

Disclosure of Interest: None Declared

Keywords: Otitis Media
A Retrospective Analysis and Comparison of the STAM and STAMCO Classification and EAONO/JOS Cholesteatoma Staging System in Predicting Surgical Treatment Outcomes of Middle Ear Cholesteatoma

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Introduction: To uniformly report the extension of cholesteatoma, to inform patients on prognosis, and to compare results of surgery, there is a great need for a cholesteatoma classification system. In 2017, the European Academy of Otology and Neurotology (EAONO) and the Japan Otological Society (JOS) published the joint consensus statements on the definitions, classification, and staging of middle ear cholesteatoma. In this statement, the STAM classification and a subsequent EAONO/JOS staging system were proposed. In the STAM classification, the middle ear and mastoid region are divided into four sites to simplify the description of the cholesteatoma extension. Merkus et al. adjusted the STAM classification by further defining the anatomical borders of those sites and by including the complications caused by the cholesteatoma (C) and perioperative ossicular chain status (O), resulting in the STAMCO classification. The classifications aim to facilitate an accurate comparison of outcome in cholesteatoma surgery and could also have a prognostic value for predicting recurrent and residual disease. Furthermore, these instruments may be potential predictors in postoperative hearing.

Objectives: The primary aim of this study is to evaluate and compare the STAM classification, STAMCO classification, and EAONO/JOS staging system as predictors for recurrent and residual cholesteatoma after primary surgery for cholesteatoma in a clinical setting using data from a tertiary referral center. Secondary, we aim to evaluate the predictive value of the classifications and staging system for postoperative hearing.

Methods: Two hundred thirty-one patients who underwent canal wall up (CWU) or canal wall down (CWD) surgery without obliteration for primary cholesteatoma between 2003 and 2013 were included and retrospectively classified and staged according to the STAM classification, STAMCO classification, and EAONO/JOS staging system. Data on cholesteatoma recidivism rates and postoperative hearing were collected. The predictive value of the three instruments for recurrent and residual cholesteatoma was compared by using receiver operating characteristic curves.

Table: Results: For predicting recurrent cholesteatoma, the STAMCO classification was significantly superior compared to the other two instruments. For predicting residual cholesteatoma, the STAMCO classification was superior to the EAONO/JOS Staging system.

When analyzing for postoperative hearing in the CWU group, an increasing extension of cholesteatoma according to all three classification was associated with a larger post-operative air-bone gap.

Conclusions: Based on our study, the STAMCO classification represents the best available predictor for recurrent cholesteatoma and holds most promise for predicting residual cholesteatoma. Extension of cholesteatoma seems to be
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linked to postoperative hearing and thus the classifications and staging systems may be able to predict postoperative hearing. More studies are needed to assess the validation of these classifications.

Disclosure of Interest: None Declared

Keywords: Cholesteatoma, recurrence, CT-scan, MRI, second-look, pediatric
Betahistine prescribing practices in England - an analysis of prescribing and national spending pre and post BEMED Trial

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Introduction: Meniere's disease is a vestibular disorder characterised by fluctuating sensorineural hearing loss, aural fullness, tinnitus and episodic vertigo. Betahistine is a strong H3 antagonist and weak H1 agonist licenced for Meniere's disease-like symptom complexes. It is relatively inexpensive and well tolerated. The 2016 BEMED trial was a multicentre, double-blind, randomised, placebo controlled, three arm, parallel group phase III dose defining superiority trial conducted in 14 German centres which concluded that long term prophylactic treatment with betahistine does not change the time course of vertigo episodes related to Meniere's disease compared with placebo.

Objectives: To establish prescribing practices of clinicians in England related to betahistine and to assess if there has been any change in prescribing practices since the publication of the results of the 2016 BEMED trial.

Methods: We accessed the English Prescribing Dataset which is published by NHS Business Services Authority. The data relates to all prescriptions issued in England and dispensed in England, Wales, Scotland, Guernsey, Alderney, Jersey and the Isle of Man. Data excluded included all prescriptions issued and dispensed in prisons, hospitals and private prescriptions.

The data was searched from Jan 2014 to Feb 2021 using the "BNF_CHEMICAL_SUBSTANCE" code 0406000B0 to include all prescriptions of betahistine 16mg, betahistine 8mg, Serc 16mg, Serc 8mg and betahistine 8mg/5ml oral suspension. Each tablet or bottle of solution was counted as a single unit. Data captured included total quantity prescribed, net ingredient cost, actual cost as well as the region and primary care organisation.

Data was compared pre and post the publication of the BEMED trial (January 2016). We also undertook a survey of UK otolaryngologists via ENT UK to ascertain whether there was widespread awareness of the results of the BEMED trial and to gain insight into specialist prescribing practices.

Results: The average monthly prescribing of betahistine from January 2014 to February 2016 was 11,294,848 units. (range = 10,280,942 - 12,276,423). The average monthly prescribing of betahistine from February 2016 to February 2021 was 11,081,123 units (range = 10,056,516 - 11,915,707). The average monthly actual cost of betahistine from January 2014 to February 2016 was £279,264.82 (range = £194,389 - 363,399). The average monthly actual cost of betahistine from February 2016 to February 2021 was £428,846.22 (range = £182,997 - £1,228,901).

We received responses to the survey from 42 otolaryngologists. All treated patients with Meniere's disease and 62% were an Otology/Neurotology specialist. Only 45% were aware of the BEMED trial and 90% prescribed betahistine for Meniere's disease.
Conclusions: There has been no significant decrease in the prescribing of betahistine since the publication of the BEMED trial and there has been an increase in the actual monthly cost of the drug. In the current economic healthcare climate, we as clinicians must use the best evidence available to inform our prescribing practice and therefore provide the best care both for our individual patients but also the population as a whole.

Disclosure of Interest: None Declared

Keywords: dizziness, Pharmacotherapy, tinnitus, Vertigo
**Evaluation of Efferent Auditory System in Patients with Multiple Sclerosis**

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**Introduction:** Auditory abnormalities can be observed in multiple sclerosis (MS) (1, 2). Afferent auditory abnormalities are well defined in MS, however there is little information about efferent auditory abnormalities in these patients (3-7).

**Objectives:** This study aims to evaluate the efferent auditory system by medial olivocochlear (MOC) reflex on patients with MS.

**Methods:** Fifty three participants with normal hearing (23 participants in control group and 30 in MS group). MS patients were divided in two groups as “patients without definable brainstem lesion (Group 1, n=15)” and “patients with definable brainstem lesion (Group 2, n=15)”. All participants had been evaluated with pure tone audiometry, tympanometric measurement, acoustic reflex test and transient evoked otoacoustic emissions (TEOAE). MOC pathway was evaluated with contralateral suppression of TEOAE (8-10). Firstly MS patients and control group’s findings were compared. Afterwards another comparison was performed for MS patients with and without brainstem lesion. A p value < 0.05 was considered as statistically significant.

**Results:** There was no statistically significant difference between pure tone thresholds of the three groups (p>0.05). TEOAE signal to noise ratio (SNR) amplitudes in right ear for 2000 and 2800 Hz were found to be higher on control group than Group 2 (p<0.05). In the left ear, SNR amplitudes with 4000 Hz in Group 1 and control group were higher than group 2 (p<0.05). There were no statistically significant difference found among three groups for MOC reflex positivity ratio in both ears (p>0.05). Mean suppression values on the control groups of left side found to be higher than group 2 left ears (p<0.05).

**Conclusions:** MS plaques may locate around brainstem and can affect the medial olivocochlear (MOC) pathway (6, 11). Our results demonstrate TEOAE SNR amplitude reduction in MS patients with brainstem involvement. Even though there is no MOC reflex positivity ratio significant difference found between groups, control group suppression level on left found to be superior to group 2. In MS patients, due to the brainstem involvement, TEAOE SNR amplitudes and suppression levels may decrease (6, 11). This research may be a baseline for further studies in MS patients, which can be a possible prognostic factor for brainstem involvement.

**References:**

Disclosure of Interest: None Declared

Keywords: efferent auditory system, MOC reflex, multiple sclerosis, olivocochlear pathway
**A review of UK cochlear implant hearing outcomes for patients with neurofibromatosis type 2**

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**Introduction:** The majority of patients with neurofibromatosis type 2 (NF2) become deaf and the management of their hearing is often complex. Historically there has been a reluctance to consider cochlear implants in patients with profound deafness and stable tumours due to concerns that retrocochlear disease would result in a poor outcomes but evidence is now to the contrary.

**Objectives:**
To review the outcomes of cochlear implants (CI) in patients with neurofibromatosis type 2 (NF2) in a large cohort, and identify factors associated with poor hearing benefit.

**Methods:**
**Study design:**
15-year retrospective national observational case series

**Setting:**
United Kingdom regional NF2 multidisciplinary teams.

**Patients:**
Consecutive patients with NF2 receiving a CI.

**Interventions:**
CI for hearing rehabilitation.

**Main outcome measures:**
1) Audiometric performance at 9-12 month after implantation using CUNY (City University of New York) sentence recognition score, and BKB (Bamford-Kowal-Bench) word recognition score in quiet (BKBq), and in noise (BKBN).
2) CI use at most recent review.

**Results:** 64 consecutive patients, median age 43 years, were included. 9-12 month mean audiometric scores were: CUNY 60.9%, BKBq 45.8%, BKBN 41.6%. There was no difference in audiometric outcomes between VS treatment modalities. After a median 3.6 years, 76.3% with available data were full or part time users. Between 9-12 month and most recent...
review there was an interval reduction in mean audiometric scores: CUNY 12.9%, BKBq 3.3%, BKBn 4.9%. Larger tumour size and shorter duration of profound hearing loss were the only variables associated with poorer audiometric scores. Tumour growth at the time of surgery was the only variable associated with CI non-use. Individual patient response was highly variable.

Conclusions: CI can provide significant and sustained auditory benefits to patients with NF2 independent of tumour treatment modality, with the majority of those implanted becoming at least part-time users. Larger datasets are required to reliably assess the role of independent variables.

Disclosure of Interest: None Declared

Keywords: case series, Cochlear implant, hearing rehabilitation, neurofibromatosis
Central vestibular disorders following head injury

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Introduction: Traumatic brain injury (TBI) and dizziness is common sequel associated with fall, contusion and motor vehicle accidents. Organic causes for post traumatic dizziness are primarily peripheral than central.

Objectives: The aim of this study is to compare and contrast the findings in those with a central versus peripheral vestibular disorder following head injury.

Methods: The UHN WSIB neurotology database (n=4291) between 1998 and 2018 was retrospectively studied for head injured workers presenting with dizziness who had identifiable central and peripheral vestibular disorders exclusive of positional vertigo. All patients had a detailed neurotological history and examination, audiometry and vestibular testing that included video nystagmography and cervical vestibular-evoked myogenic potentials. Imaging studies including routine brain and high resolution temporal bone CT scans and/or intracranial MRI were available for the majority of injured workers. Statistical analysis was performed using SPSS 21 for Mac OsX, (SPSS Inc., Chicago, IL, USA). Descriptive statistics for continuous variables included mean and range and for categorical variables the frequencies were calculated. Chi-square test assessed significance of data difference. The level of significance was P<0.05.

Results: Among the 4291 head injured workers with dizziness, 23 were diagnosed with a central vestibular disorder and 244 with a peripheral vestibular disorder. The mechanism/severity of head injury, intracranial imaging, laboratory audiovestibular findings and the clinical presentation of those with a post traumatic central vestibular disorder were reported and compared against head injured workers with peripheral vestibular dysfunction.

Conclusions: Post traumatic central vestibular injury is relatively uncommon. It usually occurred in those following high impact trauma and was reflective of a more severe head injury where shearing effects upon the brain resulted in diffuse axonal injury. Complaints of imbalance and ataxia seemed more common than complaints of vertigo. A number of other statistically significant differences were also identified between the two groups. Eye movement abnormalities were highly indicative for central nervous system injury even in those with minimal change on CT/MRI.

Disclosure of Interest: None Declared

Keywords: Dizziness; Central vestibular disorders; Imbalance; Trauma
Introduction: Hearing loss ranks 3rd in the 2019 Global Burden of Disease rankings for “years lived with disability” with the majority of those affected living in low- and middle-income countries. [1] Whilst the negative effects of living with chronic disability are well described there has been little previous work exploring the disease-specific quality of life (QoL) of patients with chronic ear disease (CED) in South Asia.

Objectives: To use qualitative research methods to explore the impact of CED on QoL in Nepal.

Methods: 20 face-to-face semi-structured qualitative interviews were conducted at the BRINOS Ear Care Centre (BECC), Nepalgunj, Nepal during a visiting ear camp in March 2019. Interviews were recorded, transcribed and translated with thematic analysis performed manually by two researchers through a process of data familiarisation, preliminary theme identification, open coding, framework construction and indexing.

Results: Five overarching themes were identified. CED has a significant impact on social interactions, emotional well-being and functionality. Healthcare seeking behaviour is varied and some participants describe no access to secondary care. Barriers to surgery are cost, accessibility, reputation, female sex and fear of complications. For patients, surgery is a means of achieving symptom control which in turn seems to be associated with a better life across all domains.

Conclusions: This study provides valuable new insight into patient perspectives on living with CED in Nepal. Patients with CED experience discrimination and stigmatisation across all levels of personal, family and social life with their function across all domains being directly limited by symptoms. Effort should be made to improve education and awareness across communities in order to encourage health-seeking behaviour, early diagnosis and reduction of stigmatisation.


Keywords: Chronic ear diseases, Global Surgery, Quality of life