#### <sup>1</sup> 7<sup>th</sup> International Symposium on **Menieve's Disease** and **International Symposium on Bisease Bisea**



**ABSTRACT BOOK** 

ORAL COMMUNICATIONS POSTERS

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# ANTISECTORY FACTOR - A CLINICAL INNOVATION IN MENIERE'S DIEASE?

## ANTISECRETORY FACTOR AND MEDICAL FOOD - NOVEL THERAPY CONCEPTS

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The antisecretory factor (AF) is a protein secreted in plasma and other tissue fluids in mammals. This 41-kDa protein provides protection against diarrheal diseases and intestinal inflammation. The endogenous plasma level of AF is increased by enterotoxins and also by certain food constituents. Based on these findings, AF-inducing medical and functional food and feed products have been developed. One of these products is named SPC, Specially Processed Cereals. Tests with this product showed it to be effective in reducing diarrhea in various animal species. In human clinical trials SPC stimulates the production of the AF protein in patients suffering from IBD, reduces their symptoms and improves their quality of life. In further clinical trials in Crohn's disease, secretory diarrhea and short bowel syndrome, SPC has been shown to exert both antisecretory effects (by inducing AF) and anti-inflammatory effects. Because of the effects on hyper-secretion in the GI tract, it was hypothesized that antisecretory treatment with SPC could be valuable in other instances where fluid imbalance is thought to play a role, such as MD. In an open pilot study, 24 MD patients received SPC for 14-30 days, and AF levels in plasma increased by 83 % in 20 of the 24 patients. The attacks of rotatory vertigo were reduced in 12 patients and in three of them hearing was normalized (Hanner et al, 2004). In a follow-up study, 51 adult patients with MD were included in a double-blind, placebo-controlled trial. 27 subjects were treated with SPC and 24 with control cereals for 3 months. The severity of MD was classified according to the AAO-HNS grading system. 14 of the 27 patients in the SPC group reported decreased vertigo, compared with 2 of 24 in the control group (Hanner et al, 2010). SPC is not a common dietary supplement. According to the EU Commission Directive 1999/21/EG of March 25, 1999, SPC is classified as a "Food for special medical purposes", i.e. food developed for specific patient Groups. SPC has been approved by the National Food Administration in Sweden, and the health claim that has been accepted is "For the nutritional treatment of disorders in connection with increased intestinal secretions".

### ANTISECRETORY FACTOR-INDUCING THERAPY IMPROVES PATIENT-REPORTED FUNCTIONAL LEVELS IN MENIERE'S DISEASE

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OBJECTIVES: The aim of this study was to evaluate the effectiveness of specially processed cereal (SPC) as a suitable adjunctive treatment for Meniere's Disease. METHODS: We performed a randomized double-blinded, placebo-controlled, crossover study in a tertiary referral center of patients who had a diagnosis of Meniere's Disease based on the guidelines of the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS). The main outcome measure was the AAO-HNS Functional Level Scale (FLS). RESULTS: Thirty-nine patients completed the study without any reported complications. The mean pretreatment FLS score for the entire study cohort was 3.8 (median, 4; range, 1 to 6). The overall FLS score improved significantly (p < 0.001), to 2.8 (median, 3), after SPC treatment. No patients showed worsening on the FLS during SPC or placebo treatment. Of the 39 patients, 23 showed improvement on the FLS, and no change was observed in the remaining 16. The median improvement on the FLS in these 23 patients was 2 points (mean, 1.7; range, 1 to 4). The mean FLS score after placebo cereal treatment was not significantly different from baseline (p = 0.452), but was significantly higher than that after SPC treatment (mean, 3.7; p < 0.001). The marginal difference observed between the baseline FLS score and the placebo FLS score was due to the fact that 5 patients reported 1-point improvements on the FLS after placebo treatment. Nevertheless, significantly fewer patients improved on placebo than on SPC (p < 0.001). CONCLUSIONS: Treatment with SPC appears to be well tolerated by most patients (91%) without any complications. More than half (59%) of the study cohort reported subjective improvement in functional level.

#### SPC FLAKES IN PROPHYLAXIS OF MENIERE'S DISEASE

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Introduction: A raised endolymphatic pressure (hydrops) is the commonly accepted pathophysiological mechanism leading to MD. A disorder of fluid and ionic homeostasis has been postulated as a causal factor leading to hydrops, and among prophylactic measures in MD diuretics are widely suggested. Antisecretory Factor (AF) is a 41 kDa endogenous protein; in different studies demonstrated the constitutive capacity of modulating fluid and ionic transport through membranes. SPC-Flakes have been clinically shown to support cellular fluid balance stimulating the body's own production of protein AF. Purpose of our work was to assess a possible effect of SPC Flakes in prophylaxis of MD.

Material and Methods: Twenty five patients with definite MD have been included in the study, consecutively recruited in 2 University centres among those poorly responsive to betahistine 48 mg /day in the previous 3 months. During the next 3 months they underwent a combined therapy with betahistine and SPC Flakes (1 gr/Kg day). Exclusion criteria were ongoing therapies with calcium channel blockers, diuretics and drugs active on Central Nervous System (SSRIs and benzodiazepines among them). Main outcome was the number of vertigo spells (per month) in the 6 months before and in the 3 months of combined therapy. An Efficacy Index (EI) was calculated with the formula y/x per 100, where y is the number of vertigo spells (per month) during combined therapy and x the number of vertigo spells (per month) in the 6 previous months. Better results are expressed by lower rates. Results: vertigo spells reduced from  $1.8\pm0.7$  to  $0.6\pm0.3$  per month (p $\leq$ 0.001). Particularly, 8 subjects presented an EI lower than 25% (32%), 8 (32%) in the range between 25% and 50%, 5 (20%) in the range between 50% and 75% and 4 (16%) higher than 75%. Audiometric exam didn't demonstrate significant changes after combined therapy. Moreover, 4 subjects (16%) reported an overall reduction of the duration of vertigo spells.

Conclusions: our data confirm those of previous works reporting a significative reduction of vertigo spells during therapy with SPC Flakes. Above all, in our sample 16 out of 25 patients demonstrated a significative response to SPC Flakes.



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# BPPV – CAN WE MANAGE ALL WITH REPOSITIONING MANEUVERS?

PATHOPHYSIOLOGY OF BPPV. WHAT HAPPENS TO OUTLETS IN THE SSC IN LONG TERM IF NOT REPOSITIONED

M. Kameswaran India

# IS THERE ANY PLACE FOR MEDICAL TREATMENT IN BPPV? HOW MUCH DO VITAMIN D LEVELS AFFECT?

F. A. Guneri Izmir. Turkey

The optimal concentration of serum vitamin D is defined by the 25-hydroxyvitamin D level and the prevalence of vitamin D deficiency/ insufficiency was reported to be around 60 % in the normal population. Vitamin D insufficiency and serum 25-hydroxyvitamin D level < 30 ng/ ml increases the risk of osteoporosis. Recent studies pointed to an association between vitamin D deficiency, osteoporosis and benign paroxysmal positional vertigo (BPPV), suggesting that an abnormal calcium metabolism may be an underlying condition. Since the level of vitamin D was found to be low in BPPV patients, it was speculated that an increase in calcium resorption may reduce the capacity of the otoconia being dissolved in endolymph leading to an increased concentration of free calcium. It was also reported that BPPV recurrences may be treated with vitamin D supplementation.

Establishment a definite pathogenetic link between low serum vitamin D level and BPPV requires animal experiments; in addition, prospective randomized controlled clinical trials evaluating the preventive effects of vitamin D supplementation on BPPV recurrences are necessary before making a paradigm shift in the treatment of BPPV.

## POSTERIOR CANAL INVOLVEMENT. HOW IS IT DIAGNOSED AND TREATED. WHY DOES IT OCCUR SO OFTEN?

M. Mandalá

Siena, Italy

Benign paroxysmal positional vertigo (BPPV) is certainly the most common cause of vertigo in adults. The lifetime cumulative incidence in the general population amounts to about 10%. The posterior semicircular canal is by far the most commonly responsible for BPPV, as it is the most gravity-dependent. The increasing interest of otolaryngologists and neurologists has led to a progressive advance in the knowledge of this labyrinthine disorder with regard to its epidemiologic, pathophysiological, clinical, and therapeutic aspects. Despite the often-effective diagnosis and treatment of most cases of BPPV, the pathophysiological explanations of the disease are mainly speculative. The posterior canal is by far the most frequently affected canal in patients with BPPV, and canalolithiasis is by far the mechanism most usually responsible. The Dix-Hallpike test is the technique most used to detect it. This maneuver brings the ampulla to a higher position with respect to the canal and the canal is aligned with the plane of movement, so favoring action of the gravity vector on any debris inside the canal. It is advisable to test the left side first, since right posterior canal-BPPV is more probable, and always to perform the test bilaterally, so as not to miss a bilateral BPPV, especially after a trauma. Posterior canal-BPPV is treated by Epley's canalith repositioning procedure or Semont's liberatory maneuver. Both procedures are safe and effective in 80–90% of cases, despite that the Epley's maneuver is a class A recommended treatment for posterior canal BPPV while the Semont's maneuver is a class B recommendation do to the lack of one more class I study. Atypical and rare variants of posterior canal involvement such as cupololithiasis or positional down-beating nystagmus will be discussed with special emphasis on pathophysiology, clinical pictures and possible treatments.

# LATERAL SSC APOGEOTROPIC NYSTAGMUS. WHAT IS THE DIFFICULTY IN IT? WHY DO NEW MANEUVERS COME OUT. WHAT IS THE BEST TREATMENT

D. Nuti Siena, Italy

It is well known that LC-BPPV can be divided into two variants, the more common one with geotropic nystagmus and the less common with apogeotropic nystagmus.

Direction-changing geotropic positional nystagmus (PN) is always, or almost always, due to canalolithiasis of the Lateral Canal and no differential diagnosis is required.

The pathophysyology of the apogeotropic variant is more debated. The most popular theory is that of cupulolithiasis, where a mass on the cupula of the LC determines its deflection by gravity. An alternative theory proposes that canalolithiasis is also able to determine apogeotropic nystagmus, if debris are located near the ampulla of the lateral canal, on its anterior part, and moving in the opposite direction with respect to the geotropic variant.

Moreover, horizontal apogeotropic PN may be occasionally due to a central vestibular lesion. The most common mimics of peripheral PN are the demyelinating and small ischemic lesions in the cerebellum or in the structures around the fourth ventricle. Differentiating peripheral from central causes of apogeotropic PN is usually easy: symptoms and signs are relatively stereotyped and symptoms and signs pointing towards central lesions are absent. Moreover, there are some nystagmus behaviors and features that provide useful information for differential diagnosis. The nystagmus characteristics can also be helpful in trying to figure out if otoconial debris are free to move in the endolymph of the LC or if they are attached to its cupula. Appropriate the generation of the same physical maneuvers/positions used to treat the generation form; Barbecue rotation, Gufoni's maneuver and Forced Prolonged Position. One option is to convert the positional nystagmus into the more treatable geotropic variant, by changing the position of debris in the canal (two steps treatment). There is also the possibility of a one-step treatment with a modified Gufoni's maneuver.

## ARE THE CANALITH REPOSITIONING MANEUVERS EFFECTIVELY TREAT BPPV ONCE? WHAT TO DO FOLLOWING THE MANEUVER? ARE THERE ANY PRECAUTIONS TO BE INSTRUCTED THE PATIENT? WHEN SHOULD WE CONSIDER SURGERY?

V. Darrouzet Bordeaux, France

The efficiency of canalith repositioning maneuvers is depending on the involved canal. In posterior canal BPPV we do consider using the Semont's maneuver as the first-line treatment, excepted in elderly patient in whom we prefer using Epley maneuver. Patients are cured in a high percentage of case (80%). In case of incomplete results or recidivism we try another maneuver again. If not effective, we perform a complete neurotological work-up leading to an MRI, since in 1 or 2% of cases affected patients have either a tumor of the cerebello-pontine angle and/or internal acoustic meatus, mostly vestibular schwannoma or an ischemic or inflammatory process in the vicinity of vestibular nuclei... In typical geotropic lateral canal BPPV, we use the barbecue maneuver, which seems to us the most effective. When facing apogeotropic BPPV we prefer performing an MRI, since a high percentage of patients may suffer from central diseases. In the quite rare and difficult problem of anterior canal BPPV, difficult to diagnose and to treat, there is no consensus on how to manage them. Mostly, the natural evolution of the disease helps to cure the patient. In this pattern, we systematically use a complete work-up.

The patient counseling is of paramount importance following maneuver. We will explain our handling. Surgical treatment is rarely necessary in our experience in typical BPPV. It must be considered when it is due to anterior canal dehiscence, Chiari malformation or cerebello-pontine tumor.





# **KEYNOTE LECTURE 1**

#### THE HISTORY OF MENIERE'S SYMPOSIUM

David J. Lim

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The antisecretory factor (AF) is a protein secreted in plasma and other tissue fluids in mammals. This 41-kDa protein provides protection against diarrheal diseases and intestinal inflammation. The endogenous plasma level of AF is increased by enterotoxins and also by certain food constituents. Based on these findings, AF-inducing medical and functional food and feed products have been developed. One of these products is named SPC, Specially Processed Cereals. Tests with this product showed it to be effective in reducing diarrhea in various animal species. In human clinical trials SPC stimulates the production of the AF protein in patients suffering from IBD, reduces their symptoms and improves their quality of life. In further clinical trials in Crohn's disease, secretory diarrhea and short bowel syndrome, SPC has been shown to exert both antisecretory effects (by inducing AF) and anti-inflammatory effects. Because of the effects on hyper-secretion in the GI tract, it was hypothesized that antisecretory treatment with SPC could be valuable in other instances where fluid imbalance is thought to play a role, such as MD. In an open pilot study, 24 MD patients received SPC for 14-30 days, and AF levels in plasma increased by 83 % in 20 of the 24 patients. The attacks of rotatory vertigo were reduced in 12 patients and in three of them hearing was normalized (Hanner et al, 2004). In a follow-up study, 51 adult patients with MD were included in a double-blind, placebo-controlled trial. 27 subjects were treated with SPC and 24 with control cereals for 3 months. The severity of MD was classified according to the AAO-HNS grading system. 14 of the 27 patients in the SPC group reported decreased vertigo, compared with 2 of 24 in the control group (Hanner et al, 2010). SPC is not a common dietary supplement. According to the EU Commission Directive 1999/21/EG of March 25, 1999, SPC is classified as a "Food for special medical purposes", i.e. food developed for specific patient Groups. SPC has been approved by the National Food Administration in Sweden, and the health claim that has been accepted is "For the nutritional treatment of disorders in connection with increased intestinal secretions".

# HUMAN PATHOLOGICAL FINDINGS

# THE HISTOPATHOLOGY OF MENIERE'S DISEASE: OBSERVATIONS FROM THE TEMPORAL BONE COLLECTION AT THE MASSACHUSSETS EYE AND EAR INFIRMARY

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The histopathology of Meniere's Disease was first described by Hallpike and Cairns and independently by Yamakawa in 1938. The histopathologic findings of hydrops has been subsequently confirmed in numerous studies since that time. The Otopathology Laboratory at the Massachusetts Eye and Ear Infirmary has processed and examined 83 ears from patients with a diagnosis of Meniere's syndrome. Observations from these studies have revealed that early in the development of Meniere's Disease, endolymphatic hydrops primarily involves the cochlear duct and saccule. However, in later stages the entire endolymphatic system becomes involved. In addition to endolymphatic hydrops, other pathologic findings include ruptures of the membranous labyrinth, fistulae of the membranous labyrinth, collapse of the membranous labyrinth and vestibular fibrosis. These findings are reviewed. These findings provide the basis for speculation regarding the underlying pathophysiology including the potential role of the endolymphatic duct and sac and the potential explanation for the symptoms of hearing loss and vertigo. Recent developments in immunohistochemistry of archival human temporal bones are beginning to shed new light on some aspects of the disease process which cannot be appreciated by standard H&E processing.

# ULTRASTRUCTURE AND IMMUNOHISTOCHEMISTRY OF THE HUMAN INNER EAR RELEVANT FOR MENIÈRES DISEASE

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During his last year Professor Heinrich Spoendlin, at the Research Department at Innsbruck University Hospital coordinated an international study of a human temporal bone obtained from a diseased patient who suffered from unilateral Menières disease (MD). Several experts gathered to unearth the root of this intriguing disease. Organ of Corti, lateral wall, including the stria vascularis, vestibular epithelia, neural portions and endolymphatic sac were thoroughly and blindly scrutinized. Several morphological changes were characterized both at the light and fine structural level. The study ended with a publication of the joint efforts. This presentation will display and summarize some of the results that were obtained. It will also give some results obtained from human inner ear studies using super-resolution immunohistochemistry with particular reference to the normal human cochlea. Obviously much remains to accomplish to better understand the fascinating microstructure and molecular composition. From these studies it is obvious that translational animal studies must be interpreted with care due to distinct variations in human and animal models. Human inner ear tissue was obtained at surgery and also at autopsy after perilymphatic perfusion. The study conforms to The Declaration of Helsinki and was approved by the medical ethical committee at the Uppsala University Hospital (2013) and Innsbruck. Patients consent was obtained.

#### CLINICAL SIGNIFICANCE OF BAST'S VALVE

A. Belal Alexandria, Egypt

The utriculo-endolymphatic valve was first described by Bast in 1928. It allows the controlled egress of endolymph from the pars superior of the labyrinth (utricle and semicircular canals) to the pars inferior (saccule and cochlea) to be processed in the endolymphatic sac.

Its presumed function is to protect the pars superior from sudden changes of pressure in the pars inferior. A reversed function may occur if sudden changes occur in the pressure of endolymph in the pars superior. Clinical and operative conditions of the inner ear are reviewed in light of these functions.





# ROLE OF HUMAN ES IN THE PATHOGENESIS OF MENIERE'S DISEASE: HUMAN TEMPORAL BONE STUDY

F. Linthicum, MD, D. J. Lim, MD Professors in Residence, Dept. of Head & Neck Surgery, UCLA Geffen School of Medicine

Number of human temporal bone studies of Meniere's patients reported the small endolymphatic duct and sac (ES) is a risk factor for MD. Based on the measurement of endolymphatic sac (ES) of 21 temporal bones (TBs) from 14 patients with history of Meniere's Disease (MD) and those of 21 (14 subjects) age-matched TBs as control group, Linthicum (unpublished data) observed the small ES is associated with the MD in comparison to non-MD ES. Volume of the human ES in MD patients varied from 0.0385 mm3 to 0.871563 (Mean=0.336803 +/- 0.669267 mm3) and Surface Area varied from 5.281421 mm2 to 108.9476 mm2 (Mean=37.2182+/- 2.167451 mm2). The volume of the ES in non-MD varied from 0.265551 mm3 to 1.451164 mm3 (Mean=0.685684+/-0.687603 mm3) and Surface Area varied from 21.83769 mm2 to 122.5041 mm2 (Mean=69.7182+/-2.056707 mm2).

It is suggested that there may be varying degree ES dysfunction or number of dysfunctional ES epithelial cells in the MD patients. It has been reported that HSV antibody in the perilymphatic fluid of the MD was found in the ES of Meniere's patients (Arnold & Niedermeyer, 1997) and also in the ES tissue of the MD patients (Welling et al., 1994). However, the ubiquitous nature of the HSV raised the skepticism for the specificity of the role of the HSV for the pathogenesis of MD. Lim and Glasscock earlier examined the ES from the 6 MD patients who undergone for the ES surgery and found evidence of focal damage of the ES and HSV-like viral particles in the neighboring cells that undergo degeneration. Furthermore, the ES are innervated by number neurons such as parasympathetic (pterygopalatine ggl.), sympathetic (superior cervical ggl.), and somatosensory (trigeminal ggl.) neurons. Thus, it is possible that latent HSV in these neuron could be reactivated by the stress and infect the ES epithelial cells causing its degeneration.

When stress is applied to these ES, they develop hydrops. Exact nature of the dysfunction is not yet understood. However, it has been shown that excessive vasopressin type-2 receptor expression in ES is associated with Meniere's Disease (Kitahara T et al, J Endocrinology, 2008).

In conclusion, the endolymphatic sac plays critical role in the pathogenesis of the Meniere's Disease.

# **KEYNOTE LECTURE 2**

# COCHLEAR PROTEOMICS OF FLUID AND ION TRANSPORT

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The determinants of inner ear fluid composition have been extensively evaluated, but fewer studies have been performed at the protein level. To address this, we assessed cochlear proteins known or suspected to be involved in endolymph and perilymph homeostasis, including the effects of normal and excessive cochlear activation, using isotopic shotgun proteomics.

Whole cochleae were harvested from FVB mice raised on a normal diet, as well as from mice reared on a diet containing only nitrogen 15 (15N). 14N mice were kept in silence, or exposed to 70, 100 or 105 dB SPL noise for 30 minutes prior to sacrifice. Protein was extracted, and individual 14N samples were spiked with a pooled 15N sample. The samples were trypsin digested and analyzed by mass spectroscopy to identify protein fragments. 14N/15N isotopic ratios were used to quantify protein levels across groups.

More than 8,000 protein traces were identified in the screen. The majority of proteins that have been implicated in cochlear fluid composition and volume regulation were represented. This included Na+/K+-, K+- and Ca2+- ATPases, Na+/H+ and Na $\pm$ /HCO3-exchangers, K $\pm$  channels, gap junction proteins, purinergic receptors and aquaporins. Changes in protein levels associated with cochlear activation were interpreted as evidence of activation followed by recycling (increases) or degradation (decreases). Of the proteins noted above, cochlear stimulation significantly altered the expression only of ion transport proteins. Isoforms of Na+/K+- ATPase, as well as Na+/H+, Na+/CO3- and Cl-/CO3- exchangers were increased, while a K+/Cl- transporter was decreased.

The results suggest that ion transport proteins in the cochlea are particularly sensitive to cochlear activation and stress. (Word count: 260)

Supported by VA grant RX000977 (AFR), Garnett Passe and Rodney Williams Memorial Foundation Research Fellowship (AW) and NIH grant DC013505 (JNS).

# PATHWAYS TO THE INNER EAR

# GENTAMICIN DISTRIBUTION IN THE EAR FOLLOWING LOCAL APPLICATIONS

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It has generally been assumed that intratympanic gentamicin enters perilymph of the ear through the round window (RW) membrane. In this study, perilymph kinetics of gentamicin was quantified by direct measurements following local gentamicin applications to the ear.

Solutions of gentamicin were applied to the guinea pig ear by two methods. The first, to establish elimination kinetics, was by injection from a pipette sealed into the lateral semi-circular canal (LSCC). As the cochlear aqueduct provides the outlet for flow, this loads the entire perilymphatic space with drug. In the second method, gentamicin solution was applied to the RW niche area. In both cases,  $10 \times 2 \mu L$  samples of perilymph were subsequently collected from the LSCC and analyzed by spectrophotometric mmunoassay (Coulter) to quantify gentamicin distribution in the ear.

Following LSCC injection of gentamicin, perilymph was sampled either immediately or after delays of 1, 2 or 4 hours. The decline of gentamicin with time was dominated by concentration decrease in the basal part of scala tympani (ST), consistent with CSF-perilymph interactions (dilution by slow entry of CSF into ST and pressure-induced oscillations across the cochlear aqueduct). In separate experiments, perilymph was sampled 1, 2 or 4 hours after application of gentamicin to the RW niche. Gentamicin concentrations were highest in initial samples (originating in the vestibule and scala vestibuli (SV)) and lower in samples originating from ST. These data confirm that gentamicin enters the vestibule directly in the vicinity of the stapes as well as through the RW. Gentamicin entry was simulated in a computer model incorporating the rapid decline in ST due to CSF interactions. This analysis confirmed that more gentamicin entered the RW compared to the stapes, but even with higher entry, lower concentrations were generated in ST due to CSF interactions influencing the kinetics. These studies show that gentamicin levels in the vestibule are substantially higher than those in the cochlea following RW niche applications, contributing to the preferential vestibulotoxicity of the drug. Nevertheless, the different physical processes affecting drug concentrations in SV and ST need to be considered in accounting for the distribution.





7<sup>th</sup> International Meniere's Disease **Inner Ear Disorders** 



# DRUG DELIVERY VIA THE OVAL WINDOW

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It has been thought until recently that the round window (RW) was the main route of entry into the inner ear following the application of therapeutic agents to the middle ear. More recently it has emerged that the oval window (OW)/stapes footplate is also an important pathway for drug delivery to the inner ear.

MRI scanning has demonstrated that gadolinium derived contrast agents (GDCA) can be seen within both the vestibular and the cochlea within one hour when applied to the round window/stapes niche of experimental animals. This raised the possibility that GDCA entered the inner ear via the stapes, in addition to the round window. We went on to test this directly by assessing the concentration of the solute trimethylphenylammonium (TMPA) within the fluids of the inner ear after its selective application to either the RW or the OW. Perilymph TMPA levels were measured using ion-selective microelectrodes sealed into the otic capsule or in perilymph samples collected from the lateral semi circular canal. Analysis of these data indicated that large portions of GDCA (up to 90%) and TMPA (30-40%) entered the inner ear via the OW. Similar recent studies with gentamicin indicate higher gentamicin levels in the vestibule and entry characteristics comparable to those of TMPA (see presentation by Salt et al.)

We have turned our attention to potential therapeutic ramifications of these findings. We have reasoned that it might be possible to preferentially target either the vestibular system or the cochlea by targeting drug to either the OW or the RW, respectively. In the treatment of Meniere's Disease this might mean that an optimal dosage of gentamicin could be delivered to the vestibule, potentially reducing the concentration in the cochlea thus reducing the risk of inadvertent ototoxicity. In early experiments, we applied a high concentration of gentamicin onto the OW or RW. Gentamicin applied to the OW induced significantly higher levels of ototoxicity. New data now show that targeted application of a lower dosage of gentamicin on the OW can result in a reduction of vestibular function while avoiding elevations in hearing threshold.

Next, gentamicin (1 uL of 5 mg/mL) was applied directly onto the OW in adult guinea pigs. One and two weeks following this procedure, short latency vestibular evoked potentials (VsEP) in response to linear head acceleration were recorded with an electrode located in the facial nerve canal. Auditory function was assessed by recording auditory evoked potentials (AEP) in response to pure tone pips (2-32 kHz) using the same electrode. Two weeks after treatment, there was a 64% reduction in VsEP amplitude without elevations in AEP threshold in gentamicin-treated animals.

These findings suggest that the risk of ototoxicity during local gentamicin therapy for Meniere's Disease could potentially be reduced by targeting a low dosage of gentamicin onto the OW. This could be achieved by injection of gentamicin to the OW under direct vision with an endoscope, or potentially with self-gelling polymers injected through the tympanic membrane. A reliable clinical implementation would need to control for the possibility that mucosal folds could obstruct the passage of drug to the oval window niche, and this latter consideration might influence whether liquid or gel-like preparations were employed.

# **KEYNOTE LECTURE 3**

# HUMAN ENDOLYMPHATIC DUCT SYSTEM. TRANSEPITHELIAL WATER CHANNELS AND COCHLEAR ULTRASTRUCTURE

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Meniere's disease (MD) continues to defy and confound the clinical/scientific community more than 150 years after its original description. Already Guild (1927), Portman (1927), Hallpike and Cairns (1938), Yamakawa (1938) and Kimura and Schuknecht (1965) suggested that MD is caused by a dysregulation of endolymph. Yet, the mechanisms by which endolymph quantity and composition are regulated and the molecular mechanisms governing water permeation across the duct epithelium remain elusive. The finely tuned hair cells and cilia mechanotransduction would seem to impose extraordinary homeostatic demands for regulation of water and ion balance (osmotic pressure), metabolic exchange and the extra-cellular DC potential. The restricted longitudinal flow of endolymph towards the sac (Salt et al. 1986) is ambiguous and how endolymphatic duct obstruction produces hydrops needs further explanation. AVP/V2R complex may play a significant role in local fluid homeostasis by controlling the elimination/reabsorption of fluid in the inner ear through stimulation of V2 receptors to mobilize AQP water channels, similar to the kidney. This could spotlight a novel therapeutic strategy. Human immunohistochemistry and in silico simulations suggest exceptionally high osmotic water permeability coefficients for the epithelial region of outer sulcus cells in the cochlear apex co-expressing AQP4 and AQP5. It could pin-point an aqueous pore-facilitated "water shunt" located in the human cochlear apex (Eckhard et al. 2014). Experimental findings and results from recent studies of the human inner ear in our laboratory will be presented relevant for water dynamics related to endolymphatic hydrops and Meniere's disease.

Human inner ear tissue was obtained at surgery. The study conforms to The Declaration of Helsinki and was approved by the medical ethical committee at the Uppsala University Hospital (2013). Patients consent was obtained





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# **BLOOD PERILYMPH BARRIER**

THE BLOOD PERILYMPH BARRIER IS VULNERABLE TO SYSTEMIC INFLAMMATION BUT IS MINIMALLY AFFECTED BY COCHLEAR MACROPHAGES

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The blood perilymph barrier (BPB) plays an important role in separating the contents of the bloodstream from the inner ear tissues and fluids. During periods of acute inflammation, solutes and free water from the blood can leak into the inner ear fluids. Vascular barrier leakiness has traditionally been viewed as an important source of cochlear dysfunction and pathology. Some have proposed that macrophages in the perivascular space play a functional role to maintain the BPB. However, what cells contribute to this barrier within the inner ear and what cells participate in barrier dysfunction is currently not thoroughly characterized.

Permeability of the BPB was evaluated in mice by applying fluorescein systemically and collecting perilymph from the posterior canal of the inner ear with an in vivo sequential sampling technique. Entry rates of fluorescein from blood into perilymph were compared for control (saline-treated) mice and endotoxemic mice (lipopolysaccharide-treated, 1mg/kg IP x 2 days). Wild-type and macrophage-depleted mice (CX3CR1-DTR mice after diphtheria toxin) were used as the animal subjects.

We found that breaches in the vascular compartment occur when experimental mice are treated with systemic lipopolysaccharide (LPS). However, in most cases, when there is marked extravasation of solute from the vascular compartment into the perilymph, there is remarkably little associated change in endocochlear potential or hearing threshold. We also found that elimination of macrophages does not render the barrier leaky, and normal barrier function and normal hearing thresholds are maintained as measured by direct perilymph sampling and ABR. In experimentally-induced endotoxemia, there was a marked increase in vascular permeability that was minimally affected by macrophage depletion despite widespread entry of cochlear macrophages into the spiral ligament and limbus in macrophage-replete animals. While the interaction between vascular permeability and inner ear fluids is likely to be important in certain cases of acquired hearing loss, the traditional belief that barrier leakiness and inflammatory cell entry alone would induce immediate loss of function requires reevaluation. In addition, what roles inflammatory cells play in the maintenance and compromise of the vascular barrier in cochlear disease will be important to our understanding of how to improve treatment for these conditions.

# THE FUNCTION OF THE ENDOLYMPHATIC SAC

# A NEW MURINE MODEL FOR MENIERE'S DISEASE - VASOPRESSIN INDUCED ENDOLYMPHATIC HYDROPS

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### The purpose of this study was to develop a more suitable animal model, having a closer resemblance to the pathophysiological process in Meniere's Disease.

Adult CBA/J or ICR mice were treated by subcutaneous injection of 50 µg/100g/day vasopressin for 5 days up to 8 weeks. Morphological analyses were performed of the cochlea, vestibular end organs and endolymphatic sac. Results. All experimental animals showed mild to moderate endolymphatic hydrops, increasing in severity as the vasopressin treatment was prolonged. Animals treated with vasopressin for 8 weeks showed severe endolymphatic hydrops with partial loss of outer hair cells and spiral ganglion cells. These animals also had a reversible vestibular dysfunction following intratympanic injection of epinephrine. We have also demonstrated that EH caused by VP recovered following the cessation of VP administration. The EH gradually increased as the VP administration was lengthened, but gradually recovered after the cessation of VP. In contrast, there was no recovery from the degeneration of cochlear hair cells and loss of spiral ganglion cells. A new murine model of Meniere's Disease has been developed, based on long-term administration of vasopressin. Induction of vestibular dysfunction in the present animal model can cause additional stress, by reducing inner ear blood flow. Our new mice model is, non surgical, more suitable animal model, having a closer resemblance to the pathophysiological process in MD, which can be widely used for the MD research.he medical ethical committee at the Uppsala University Hospital (2013). Patients consent was obtained.

# ULTRASTRUCTURE AND GENE EXPRESSION IN THE HUMAN ENDOLYMPHATIC SAC - NOVEL EVIDENCE OF MULTIPLE FUNCTIONS

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The function(s) of the endolymphatic sac and its involvement in inner ear disease remain enigmatic. To explore these issues, we applied transmission electron microscopy, cDNA microarray and immunohistochemistry to fresh human endolymphatic sac tissue samples. Electron microscopy revealed novel ultrastructural features indicative of function and the gene expression analysis showed an upregulation of genes of several functional annotations, including immune system and solute carrier family genes. Immunohistochemistry verified translation of selected genes, as well as localization of the specific protein within the sac. The unique data on human tissue support the endolymphatic sac as a pluripotent organ involved in immune defense and pressure regulation within the inner ear.



#### ION TRANSPORT IN ENDOLYMPHATIC SAC EPITHELIAL CELLS ON THE BASIS OF EXPERIMENTAL ANIMAL RESEARCHES

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The endolymphatic sac (ES) is believed to play important roles in the homeostasis of the endolymphatic system. However, ion transport system of the ES remains to be clarified. Based on recent research results in experimental animals, ion transport system in the ES epithelial cells is outlined.

Unlike cochlear and vestibular endolymph, ES endolymph has higher Na+ and lower K+ concentrations. Na+ and Cl- are dominant ions in the ES. ES endolymph has a positive DC potential of + 15-20 mV. The resting membrane potential in the ES epithelial cells is approximately - 60 mV. The electrochemical gradient across the apical membrane of epithelial cells is calculated to be a large value of + 140mV for Na+, indicating a very strong Na+ inflow from the ES lumen inside the cell. Several ion channels (outward delayed rectifier K+ channel, amiloride-sensitive epithelial Na+ channel (ENaC), Ca++ sensitive nonselective cation channel), and several ion transporters (Na+-K+-2Cl- cotransporter (NKCC), thiazide-sensitive Na+-Cl- cotransporter (TSC), Na+-H+ exchanger, Cl- - HCO3exchanger (SLC4A2), pendrin) have been reported in ES epithelia cells.

The ES intermediate portion has a stronger activity of Na+, K+-ATPase and a higher Na+ permeability in mitochondria-rich cells, strongly suggesting a higher potential of Na+ absorption from endolymph in the ES.

Several molecules relating to mineralocorticoid action such as ENaC, TSC, 11β-hydroxysteroid dehydrogenase (11βHSD), mineralocorticoid receptor have been reportedly expressed in ES epithelial cells, suggesting that ES epithelial cells may be a target tissue for mineralocorticoid hormone, which increases endolymph absorption in the ES.

The ES epithelial cells (mainly mitochondria-rich cells), which are involved in ES endolymph absorption via active sodium transport, may crucial roles in maintaining the homeostasis in the endolymphatic system.

#### POTASSIUM SECRETION VIA APICAL MULTIPLE POTASSIUM CHANNELS IN HUMAN ENDOLYMPHATIC SAC EPITHELIUM

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The endolymphatic sac (ES) has been thought to be involved in the regulation of inner ear homeostasis. So far, many ion channels, transporters, and exchangers were identified in endolymphatic sac, the exact location and the role of K+ channels have not been fully identified. The role of K+ channels on the ES must be important in regulating relatively high K+ concentration in ES luminal fluid by which ES potential is maintained. In this study, we tried to investigate K+ channels and exchangers which contribute to the regulation of K+ concentration in human endolymphatic sac. Human ES was harvested during acoustic tumor surgery via translabyrinthine approach. The candidate K+ channels were investigated by proteomic analysis (LC-MS/MS) and by measuring transepithelial current with scanning vibrating electrode technique (SVET). To verify K+ transporting ion channels and exchangers identified by SVET and LC-MS/MS, RT-PCR, and immunohistochemistry were performed. The transepithelial current from human ES epithelium was blocked by 4-AP, Ba, and apamin. The current change after application of the pharmacologic agent was significant from the concentration of 10mM 4-AP, 1mM Ba, and 100nM apamin. The current was also significantly inhibited by bumatanide (10uM) and ouabain (1mM). K+ channels with this pharmacologic properties were KCNJ13, KCNJ14, KCNK2, and KCNK6. Additional K+ channels such as KCNB1, KCNC4, and KCNH1 were identified by LC-MS/MS. Finally verified K+ channels existing in human ES epithelium by functional study, RT-PCR, and immunohistochemistry were KCNB1, KCNN2, KCNJ14, KCNK2, and KCNK6. This is the first report of apical K+ secretion in the human ES epithelium. Mutiple K+ channels including inwardly rectifying, voltage-dependent, and Ca-activated K+ channels were involved in the apical K+ secretion in human ES epithelium. NKCC and Na+,K+ - ATPase provide driving forces for the K+ secretion. This apical K+ secretion in human ES epithelium is likely to play an important role in regulating relatively high K+ concentration of ES luminal fluid and endolymphatic sac potential.

### MENIERE'S DISEASE HISTOPATHOLOGICAL ANALYSIS: NOVEL ULTRASTRUCTURAL. MOLECULAR AND MRI FINDINGS

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The pathophysiology of Meniere's Disease (MD) suggest an involvement of abnormalities affecting endolymph resorption, vascular abnormalities, post viral autoimmune, and factors related to water homeostasis. Histopathological analysis is the gold standard to determine which cells are affected in MD. In this study we performed a systematic histological and a ultrastructural analysis, complemented with molecular and immunohistochemical analysis in vestibular end organs acquired from labyrinthectomy in Meniere's Disease. We perform this study in 20 subjects with intractable MD and ipsilateral non-serviceable hearing presented in our Neurotologic clinic (average age 62, range 29-83 years old) at UCLA. The average duration of symptoms prior to surgery was 7 years (range 1-20 years). Histological analysis of thin plastic sections demonstrated varying degrees of degeneration, being the cristae more affected than the macula utricle. A monolayer of epithelial cells in the cristae, was consistently observed, in contrast the macula utricle is better preserved. We also detected a pronounced basement membrane thickening in the crista as compared to the macula utricle. Additional findings include hair cell and supporting cell vacuolization, stereocilia loss, and edema in the stroma. Transmission electron microscopic (TEM) analysis of these specimens showed disorganization of the basement membrane underneath the epithelia, normal morphology of nerve terminals and myelinated fibers. Further analysis of the vasculature showed novel ultrastructural changes in the blood labyrinthine barrier (BLB) not previously reported in the otology literature. In the BLB of capillaries in the vestibular end organs stroma we found increased transcellular vesicular transport across vascular endothelial cells, pericyte detachment and perivascular basement membrane disruption in the stroma was observed. Severe MD cases showed in addition, vacuolization of endothelial cells and/or complete atrophy. Ultrastructural alterations in the BLB from Meniere's specimen's correlates with the presence of edema in the perilymphatic space. Utricles from normal individuals obtained at autopsy showed no pathological alterations in the BLB, stromal tissue or sensory epithelia. These results suggest that alterations of the BLB maybe a contributing factor in the underlying physiopathology of MD. Recent studies using Cellular and ultrastructural changes match well with our molecular biological studies in similar type of specimens. We have detected changes in the expression of several specific inner ear proteins: Specifically down and upregulation of aquaporin 4 and 6 respectively (both expressed in supporting cells), upregulation of cochlin (expressed in the stroma) and decrease in collagen IV and laminin-1b two basement and perivascular membrane proteins. Recently, objective quantitative criteria for EH using delayed intravenous gadolinium 3D fluid attenuation inversion recovery (3D-FLAIR) MRI have been developed, and the degree of EH was significantly correlated with the degree of hearing loss. Using this technique we found that the degree of EH strongly correlated with auditory hearing loss based on the pure tone average in the setting of MD. In conclusion MD is a complex syndrome that involves histological and molecular subtracted that need to be further investigated to provide novel treatments for this debilitating disease.



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# **REGENERATION, PROTEOMICS AND GENETICS**

### HISTOLOGICAL AND FUNCTIONAL ANALYSIS OF XENOGRAFT STEM CELLS OF THE INNER EAR OF MICE IN THE GUINEA PIG COCHLEA-INDUCED HEARING LOSS

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In mammals, damage to the sensory receptor cells (hair cells) of the inner ear results in permanent sensorineural hearing loss. Here, we investigate whether postnatal mouse inner ear progenitor/stem cells (mIESCs) are viable after transplantation into the basal turns of neomycin-injured quinea pig cochleas. We also studied the potential effects of the cell transplantation on auditory function. Eight adult guinea pigs were deafened by intratympanic neomycin delivery. After 7 days, the animals were randomly divided in two groups. The study group (n=4) received transplantation of LacZ-positive mIESCs in culture media to the scala tympani. The control group (n=4) received culture media only. Fourteen days after the transplantation, functional analyses were performed by auditory brainstem response (ABR) measurement, and the animals were sacrificed. The presence of mIESCs was evaluated by immunohistochemistry of sections of the cochlea from the study group. Non-parametric tests were used for statistical analysis of the data. Intratympanic neomycin delivery damaged hair cells and increased auditor y thresholds prior to cell transplantation. There were no significant differences between auditory brainstem thresholds before and after transplantation in individual guinea pigs. Some mIESCs were observed in all scalae of the basal turns of the injured cochleas, and a proportion of those cells expressed the hair cell marker myosin VIIa. Some transplanted mIESCs engrafted in the cochlear basilar membrane. Our experiments demonstrated that transplanted cells survive and engraft in the organ of Corti after cochleostomy.

#### CHARACTERIZATION AND GENE EXPRESSION PROFILE OF AN INDUCED PLURIPOTENT STEM CELL MODEL FOR FAMILIAL MENIERE'S DISEASE

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Meniere's Disease (MD) is an inner ear disorder characterized by sensorineural hearing loss, episodic vertigo and tinnitus. Using whole exome sequencing, we have identified for the first time two mutations in the FAM136 and DTNA genes which can be candidate disease-causing genes (1). The aim of this study is to generate a cellular model of MD using human induced pluripotent stem cells (iPSCs) will help to determine the functional role of these genes in familial MD.

We have generated iPSCs from a MD patient and a healthy relative from peripheral blood mononuclear cells (PBMCs) using nonintegrative Sendai viruses containing Sox2, Oct3/4, c-Myc and KIf4 reprogramming factors (CytoTune®-iPS 2.0 Sendai Reprogramming Kit-Life Technologies). Two clones, MD-iPSCs (W7) and control-iPSCs (A2), were established and characterized in vitro and in vivo, including gene expression studies.

First, we determined that exogenous reprogramming factors were not expressed in A2 at passage 7 (p7) and W7 passage 18 (p10). Initial characterization included alkaline phosphatase staining and expression of pluripotency markers hOCT4, hSOX2, hKLF4, hMYC and hNANOG by quantitative PCR. W7 and A2 clones also expressed OCT4, SSEA4 and TRA-1-60 proteins as assessed by immunocytochemistry. Furthermore, both cell lines demonstrated pluripotency in vitro by embryoid bodies formation which differentiated into three germ layers (ectoderm, mesoderm and endoderm) and by detection of differentiation markers in in vivogenerated teratomas by immunohistochemistry. Of notice, both cell lines showed different proliferation rates, as MD-iPSCs W7 have a doubling time of 48-53 hours, while WT A2 cells divide every 36-39 hours.

Future studies with this cellular model will include in vitro differentiation towards otic precursors to repair FAM136A and DTNA mutations in differentiated cells-derived from iPSCs from FMD patients using the RNA-guide CRISPR-Cas9 system to restore the phenotype.

#### Acknowledgements

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Requena T, Cabrera S, Martín-Sierra C, Price SD, Lysakowski A, Lopez-Escamez JA. Identification of two novel mutations in FAM136A and DTNA genes in autosomal dominant familial Meniere's Disease. Hum. Mol. Genet. (2015). 24(4):1119-26.doi: 10.1093/hmg/ ddu524.o play an important role in regulating relatively high K+ concentration of ES luminal fluid and endolymphatic sac potential.

# CONFOCAL IMAGING OF STIMULUS-INDEPENDENT ACTION POTENTIAL ACTIVITY IN THE DEVELOPING COCHLEA

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Spontaneous action potential (AP) activity occurs during critical periods of mammalian sensory system development. In the mammalian cochlea, it is likely that such activity is driven by AP firing in cochlear inner hair cells (IHCs). In this work, we complemented singlecell electrophysiology with large scale optical imaging using confocal microscopy systems developed in our laboratory to investigate the relationship between spontaneous AP activity in sensory IHCs and connexin-mediated calcium transients in cochlear nonsensory cells. We found that IHCs fire action potentials even in the absence of detectable calcium waves in nearby non-sensory cells, therefore confirming that spontaneous activity is intrinsically generated in IHCs during development. Moreover, we show that calcium waves exerts a modulatory effect on IHCs firing and synchronize the simultaneous response of several nearby IHCs. We hypothesize that the synchronized response of nearby IHCs refines tonotopic maps along the auditory pathway before the onset of sensory experience.

# HES-1 AND COUP-TFI SHRNA KNOCKING DOWN GIVE RISES TO NEW HAIR CELLS AND SUPPORTING CELLS IN ORGAN OF CORTI ORGANOTYPIC CULTURE

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Notch pathway proteins, including Hes-1, play a role in keeping supporting cells phenotype and prevent them from becoming hair cells by lateral inhibition mechanism. COUP-TFI is expressed during early otic vesicle development and is correlated with the differentiation of hair and support cells in the organ of Corti. The aim of this study were to compared the expression of hair and supporting cells and quantify the mRNA levels after knocking down Hes-1 and COUP-TFI transcripts in organ of Corti organotypic cultures of postnatal day 3 mouse. 48h after lentiviral transfection, RNA from the organ of Corti was extracted from six conditions: control, scrambled, shRNA for Hes1, shRNA for COUP-TF1. Real Time PCR assess the amount of Hes-1 and COUP-TFI silencing, as well as Myo7a, Pax2, Sox2 and p27. Among the conditions willing to silence Hes1 gene, the one with the lowest level of silencing (Hes1.2 10%) showed interesting results such as increased levels of expression of Myo7a (200%), Sox2 (150%) and p27(10%). These findings suggest minor silencing of Hes1 gene leads to cell proliferation, both hair and supporting cells. On the other hand among the conditions willing to silence Coup-Tf1 gene, the one with highest level of silencing (COUP10 30%) revealed increased levels of expression of Myo7a (70%), Sox2 (60%), Pax2 (130%) and p27(40%). These findings suggest major silencing of Coup-Tf1 gene leads to cell proliferation, both hair and supporting cells, and was supported by immunofluorescence analysis of the organ of Corti cryostat sections.





#### HETEROZYGOUS MUTATIONS IN DTNA AND FAM136A GENES IN FAMILIAL MENIERE'S DISEASE

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Familial Meniere's Disease (MD) is found in 9% of cases in European population. Although genetic heterogeneity is observed, most of the families have an autosomal dominant pattern of inheritance with incomplete penetrance (1).

We investigated a family with 3 affected women in consecutive generations. DNA was isolated from human peripheral blood and whole exome sequencing (WES) was carried out in a SOLiD 5500xl platform. A bioinformatics pipeline with variant-prioritization algorithms, including phenotype ontology were used to filter and prioritize the resulting variants (2), obtaining seven candidate variants that were validated by Sanger sequencing. Morphological and functional studies including immunohistochemistry, gene expression, and immunoblotting were carried out to confirm the pathological effect of the two final candidate variants.

We have identified two novel variants: a heterozygous nonsense mutation in the FAM136A gene chr2:70527974C>T which truncates the protein by 62 AA and a second heterozygous missense mutation in DTNA chr18:32462094G>T generating a novel splice-site. Its effect was evaluated in lymphoblasts and a new mRNA isoform, missing 49 nucleotides in exon 21, was confirmed. Two FAM136A mRNA transcripts and their protein products were confirmed in patient lymphoblasts. Carriers of FAM136A mutation showed a significant decrease in the expression levels of both transcripts in lymphoblastoid cell lines (p=0.002).

FAM136A encodes a membrane protein of unknown function associated with mitochondria. In rat crista ampullaris, we have found that FAM136A protein co-localizes with the mitochondrial marker COX IV in the basal pole of vestibular hair cells. DTNA encodes alpha-dystrobrevin, a membrane protein involved in the formation and stability of synapses and the preservation of brain-blood barrier (3). In the inner ear, alpha-dystrobrevin was located in supporting cells, close to the stromal region. Preliminary results show that both proteins are presented in cochlea.

Novel mutations in FAM136A and DTNA genes are probable causal variants in familial MD. A decrease in expression of coding transcripts in patient lymphoblasts, leading to haploinsufficiency of FAM136A, and the generation of a novel splice-site in DTNA gene, skipping exon 21, suggest a functional role for both genes in familial MD.

Acknowledgements

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#### A PROTEOMICS BASED APPROACH IN MENIERE DISEASE

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Diagnosis of Meniere's Disease (MD) is still widely on clinical basis. This is caused from the fact that the pathophysiology of MD is still largely unknown, without specific signs or symptoms. Consequences are on inaccuracy in terms of epidemiology, diagnosis and treatment. We have used a proteomics-driven approach to identify potential biomarkers of MD. To this end, plasma was obtained from whole blood of 20 individuals previously diagnosed as suffering from MD and compared to plasma from healthy donors. A depletion of the highly abundant proteins (i.e. albumin, IgG, transferrin, etc.) was performed in order to enhance the chance of detection of the less represented ones, therefore reducing the noise-background. Two-dimensional gel electrophoresis, followed by in-gel tryptic digestion of the selected spots and LC-MS/MS analysis, allowed us to identify a set of proteins whose expression appears to be differentially modulated in patients vs. controls. In particular: complement factor H and B, fibringen alpha and gamma chains, beta-actin and pigment epithelium derived factor are over expressed; on the other hand, the levels of beta-2 glycoprotein-1, vitamin D binding protein and apolipoprotein-1 are significantly decreased in the plasma of MD-affected individuals. Even though preliminary and not necessarily linked directly to the molecular pathogenesis of the disease, our original findings suggest that a molecular signature, represented by the plasma protein profile previously described, might represent a potentially powerful, innovative and not invasive tool for early diagnosis and clinical management of MD patients. Moreover our findings uncover a potentially starring role for some proteins in the development and fate of this frustrating disease, whose pathogenesis still remains unclear.

## ROLE OF OXIDATIVE STRESS IN THE COCHLEAR DAMAGE IN ACQUIRED SENSORINEURAL HEARING LOSS: ANIMAL MODEL LESSON

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Sensorineural hearing loss recognizes several causes ranging from direct and prolonged acoustic trauma to administration of drugs such as streptomycin and cisplatin. The mechanisms through which these agents induce hearing loss are well understood and the role played by excessive production of free radicals, namely reactive oxygen species, and the consequent oxidative stress are no longer matter of debate. Through the adaptive stress response, cells, in particular neural cells, try to counteract free radical-induced damage and increase lifespan. The heme oxygenase-1/biliverdin reductase system (HO-1/BVR) is a main player in the cell stress response because it catabolyzes heme, toxic if produced in excess or under condition of redox imbalance, and generates bilirubin, a strong free radical scavenger. Several approaches have been proposed to activate the HO-1/BVR system and prevent/contrast neuronal damage, one of the more reliable consists in the supplementation with natural antioxidants such as ferulic acid (FA), curcumin (CUR), Coenzyme Q (CoQ), rosmarinic acid (RA) etc. Our studies demonstrated that the sub-chronic systemic administration of both FA and CUR and CoQ and RA improved auditory function in rodents exposed to noise or cisplatin with a composite mechanism of action which include an efficient free radical scavenging activity and reduced oxidative stress, particularly evident at earlier time points. Furthermore, a sustained induction of HO-1, through the nuclear translocation of the transcription factor Nrf2, is an adjunctive mechanism of neuroprotection which becomes significant at later time points. In conclusion, systemic administration of (poly) phenols and other natural antioxidants is a novel strategy to improve auditory function in subjects exposed to acoustic trauma or ototoxic drugs.

#### ALTERED CHROMOGRANIN-A CIRCULATING LEVELS IN MENIERE'S DISEASE

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Objectives: Menière's Disease (MD) is an inner ear disorder characterized by episodic vertigo, ear fullness and hearing loss; usually vertigo attacks cluster in specific periods, followed by asymptomatic periods. We studied in MD patients the circulating levels of immunoreactive chromogranin A (CqA) and its fragment vasostatin-1 (VS-1), two polypeptides secreted by the neuroendocrine system involved in the regulation of the endothelial barrier function and vascular homeostasis. Methods: Serum levels of immunoreactive CqA (full-length CqA and fragments lacking the C-terminal region) and of VS-1 were assessed in 37 consecutive MD patients and 36 controls. The ratio between VS-1 and CqA was calculated. Results: CgA levels were significantly increased in patients compared to controls (1.46±1.78 vs 0.67±0.27 nM, p=0.01), while no difference was detected for VS-1 (0.41±0.19 vs 0.39±0.18 nM, respectively). The CgA levels in patients positively correlated with the frequency of vertigo spells in the previous four weeks (p=0.008) and negatively with the time in days from the last vertigo attack (p=0.018). Furthermore, the VS-1/CqA ratio negatively correlated with the frequency of vertigo spells (p=0.029) and positively correlated with the time from the last attack (p=0.003).

Conclusion: The results indicate that variations in CgA levels, but not of VS-1, occur in the blood of patients with active MD, depending on the frequency of vertigo spells and the time from the last crisis. Considering the known effects of CqA and fragments on the regulation of vascular homeostasis, this finding may have pathophysiological implications that merit further investigation.





# SYMPOSIUM ON ELECTRICAL VESTIBULAR STIMULATION

### HIGH RESOLUTION MICRO CT SCANNING OF THE HUMAN LABYRINTH TO ASSESS ANATOMICAL VARIABILITY FOR A VESTIBULAR **ELECTRODE DESIGN**

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People who suffer from severe loss of vestibular sensation may be helped in the future with electrical stimulation by a vestibular implant. Like in the cochlea there are inter-subject morphological deviations in the vestibular system that may be relevant for the design of vestibular electrodes. To assess dimensions and variations of sensory structures, fluid spaces and nerve fibre pathways we developed methods to non-destructively image whole human temporal bones with micro computer tomography ( $\mu$ CT) at high resolution. This allows us to acquire accurate quantitative morphology of the complex inner ear structures down to few micrometer resolution at reasonable costs with commercially available µCTs.

Established for visualization of mineralized tissue the use of broad band x-rays requires contrast enhancement of soft tissue. The inner ear is a challenge for this technique since it is situated within the hardest bone (high absorption) and contains delicate membranous structures (very low x-ray absorption). We tested several contrast enhancement agents to selectively display nerve fibers and soft tissue in human and animal inner ears before and after decalcification of mineral components. Obtained data serve in a further step to evaluate deviations of with statistical shape models and finite element modeling of current spread. 35 human specimens were imaged with a SCANCO uCT40 and Carl Zeiss Xradia 400 at 70KeV for ossified and 45KeV for decalcified bones. Datasets were visualized and processed with Amira®5.5. Initial tests for contrast enhancement were done with mice, cat and human temporal bones and imaged at voxel resolutions between 3,5µm and 15µm using phosphotungstic acid (PTA), Lugol's 10% iodine potassium iodine (IKI), 1% iodine in absolute ethanol, osmium tetroxide, Tannic acid and a Megluminamidotrizoat-Natriumamidotrizoat mixture. IKI and PTA provide the highest contrast of soft tissue in ossified inner ears so that bone as well as soft tissue can be displayed within the same specimen acquired in one scan at 70KeV. This procedure is ideal for screening purposes of smaller animals (mice, rats, cats, guinea pigs, etc.) to detect anomalies of gross anatomy, bone and membranous labyrinth.

Substantial loss of nerve fibers and neurons as well as degeneration of spiral ligament and stria vascularis can be detected and volumes quantified across the whole inner ear. For human temporal bones this technique did not provide equal results with the equipment and settings used. The extremely dense bone and bigger specimen size (hence increased voxel size) impedes visualization of delicate membranous structures within the ossified temporal bone which may be an issue of dynamic range in image acquisition. OsO4 in combination with decalcification of mineral components seems to be the method of choice to selectively present myelinated nerve fibers and membranous structures together with some tissues that give higher contrast (sensory epithelium of the vestibular system and stria vascularis). Isotropic non-destructive µCT imaging is a versatile tool to assess dimensions of relevant structures for new types of vestibular electrodes and identify variability for optimal and safe electrode positioning.

#### VESTIBULAR IMPLANT FOR SENSORY RESTORATION – CANDIDACY AND EPIDEMIOLOGY

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Profound bilateral vestibular deficiency (BVD) causes disabling oscillopsia, chronic disequilibrium, and postural instability, and despite medical therapy and rehabilitation, there is no adequate treatment for individuals disabled by this loss. Affected individuals suffer illusory drift of visual fields during head movement, chronic disequilibrium and postural instability caused by failure of vestibuloocular and vestibulo-spinal reflexes. Recent epidemiologic data from a national survey of United States adults reveal that more than 64K US adults (28/100K) suffer a constellation of symptoms consistent with chronic, profound bilateral loss of vestibular sensation. Affected individuals report reduction or cessation of driving due to their symptoms (44%), a high incidence of reduced participation in social activity (56%), a >24-fold increase in fall risk in comparison to the nationwide average (Ward et al., 2013). BVD individuals

also report significantly reduced guality of life, increased health care expenses, and decreased productivity due to dizziness-related workplace absenteeism. An implantable prosthesis that continuously and accurately emulates normal sensory transduction of head rotation could significantly and cost-effectively improve quality of life for these individuals. This talk will discuss vestibular implant candidacy, cost-effectiveness and characteristics of the population of patients who stand to benefit most from this technology.

#### THE VESTIBULAR IMPLANT: TOWARDS A CLINICALLY USEFUL DEVICE

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Objective: To further assess the feasibility of a multichannel vestibular implant (VI) in patients with a bilateral vestibular loss (BVL). Methods: Multiple characteristics of the VI were investigated in 12 BVL patients fitted with a modified cochlear implant (MED-EL) providing vestibular electrodes in addition to the "standard" cochlear array: 1) Interaction of predominantly horizontal and vertical VI-input with horizontal residual vestibular function. 2) Dynamic visual acuity (DVA). 3) Perception of VI-input. Results: 1) VI-input combined with residual function produced a VOR that was the result of both inputs and in which characteristics of the strongest component dominated in the acute phase of stimulation. 2) The VI was able to significantly improve the DVA. 3) Perceptual thresholds were generally lower than VOR-thresholds, implying activation of different neural pathways. Conclusion: These recent investigations provide more evidence for the feasibility of a clinically useful VI in the near future. Since different neural pathways are stimulated, the effect of the VI should not only be objectified by evaluation of the vestibulo-ocular reflex.

#### VESTIBULAR IMPLANT: 12 YEARS OF DEVELOPMENT IN THE HUMAN

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The description of symptoms resulting from a bilateral vestibular deficit is difficult for patients and often misinterpreted by doctors. Patients do not know about the vestibular system that works unconsciously. Moreover, the vocabulary which would be needed is lacking. Therefore the diagnosis is made only after many years of wandering (more than 2.5 years in a series of 23 patients, up to 9 in one case) and numerous visits to all kinds of specialists (7 in average, up to 20). Since 12 years we are testing a vestibular prosthesis in the human. It is made of motion sensors, an electronic processor and electrodes implanted close to the ampullary organs. At the time of writing this summary, 12 patients are equipped with our artificial inner ear prototype.

We have been the firsts to show that it is possible to restore the vestibulo-ocular reflexes with a gain close to normal, allowing to correct one of the major symptoms of which the patients are complaining, a blurred vision while walking. The results obtained in the laboratory are very encouraging and suggest that it will be possible to offer a solution to patients suffering from a bilateral vestibular deficit within a few years.





7<sup>th</sup> International Meniere's Disease Inner Ear Disorder



# **KEYNOTE LECTURE 4**

## **REGENERATIVE MEDICINE FOR THE INNER EAR**

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Inner ear disorders such as sensorineural hearing loss, vertigo and dizziness and tinnitus are incurable in some occasion by conventional therapeutic strategies. New therapeutic strategies for protection or recover of inner ear function are therefore to be investigated. Latest findings on regenerative therapy for the inner ear diseases will be presented.

In the early phase of inner ear damage, we should try to rescue inner ear cells from cell death and promote self-repair activity. Together with the experimental results, result of clinical trial of local drug application using new drug delivery system (DDS) into the inner ear using neurotrophic factors or some other drugs will be presented.

Induction of cell transdifferentiation is a possible strategy. However, if no cell sources remain in the inner ear, cell transplantation then becomes another choice to restore cell growth through regeneration. The potential of several kinds of stem cells such as embryonic stem cells (ES cells), bone marrow stromal cells (BMSCs) and induced pluripotent stem cells (iPS cells) were examined as donor cells of transplantation for replacing inner ear hair cells, spiral or Scarpa ganglion neurons (cochlear and vestibular nerve) and other cells in the inner ear. Transplantation of those cells will improve auditory and vestibular function. So cell transplantation therapy is a useful method for treatment of inner ear diseases. Then as a novel therapeutic method for sensorineural hearing loss, implantation of an Artificial Auditory Epithelium will be explained.

# **AUDIOLOGICAL DIAGNOSTICS**

## ON THE ROLE ON DEPLETIVE TESTS: A REVIEW ANALYSIS

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The state-of-art of the "glycerol test" shows that even if the interest in the classic glycerol test of Klockhoff and Lindblom in the recent years is reduced, to some extent the test is still among the most used, for the diagnosis, the identification of the disease stage and, eventually, for specific therapeutical modalities. The authors evaluate the evolution of the depletive tests in the last fifteen years, in terms of: the characteristic of the different drugs used for diagnostic and therapeutic purposes in the clinical management of the endolymphatic hydrops; the administration method; and the method of evaluation of the outcome. During this period, maximum effort has been devoted to the improvement of the sensitivity and specificity of the "glycerol test" that today seems to be the most used drug that allows an objective correlation with Menière's disease. Apart from the osmotic action, other effects have been identified and proposed on different inner ear districts. The authors conclude that it would be necessary a more appropriate selection of the candidates for a depletion test in order to increase its sensitivity rate as well as to use also objective procedures (ECochG, MRI) to validate it.

# SENSITIVITY OF ELECTROCOCHLEOGRAPHY VS. OTOACOUSTIC EMISSIONS TO DISRUPTED COCHLEAR HOMEOSTASIS IN MENIERE PATIENTS

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The responses of cochlear hair cells to sound stimuli are highly sensitive to the resting environment and operating point of their stereocilia bundles, adjusted for optimal operation. Cochlear hydrops, a hallmark of Menière's disease (MD), likely disrupts stereocilia operation, with fluctuating hearing sensitivity as an expected result. For several decades, its objective diagnosis has rested upon electrocochleography. The increased size of the summating potential SP relative to the compound action potential of the cochlear nerve AP has been thought to reflect an exaggerated depolarization of hair cells in relation to a deformed, inflated scala media. Recently, otoacoustic emission (OAE) changes with body tilt have shown an abnormal behavior in the presence of MD symptoms (Avan et al, Hear Res. 2011, 277, 88-95). Here, the outcomes of SP and OAE tests performed concomitantly were compared in typical MD patients.

# USE OF MULTIFREQUENCY ADMITTANCEMETRY ASSOCIATED TO GLYCEROL TEST TO ASSESS HYDROPS - NORMATIVE VALUES IN **HEALTHY SUBJECTS**

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Hydrops and abnormalities of inner ear fluid pressure are involved in some otological disease such as Meniere's Disease. However, demonstrating presence of hydrops is challenging. It is also difficult to predict the efficiency of osmotic treatments. Using the admittancemetry tests at 2 kHz (conductance and resonance frequency) associated with glycerol test, we aimed to answer these two questions. Moreover, even if it is used since many years, glycerol test has never been assessed with normative data in healthy subjects.

The first part of this study aimed to collect normative data from 17 healthy subjects (34 ears). We obtained for all of them a complete audiometry, measurement of conductance à 2 kHz, before and 1 hour and half after an oral dose of glycerol (1,5 g/kg body weight) (concentration : 63 g/100ml). We assessed the effect on audiometry, width of conductance tympanograms at 2 kHz, resonance frequency, and the presence of clinical symptoms. The mean age of the healthy subjects was 33 + 1/2 years old. Sex ratio : 3 males /14 females. The symptoms due to glycerol ingestion were : unsteadiness (47%), nausea (71%), headaches (88%), asthenia (35%). Audiometry was unchanged after glycerol ingestion. Width of conductance tympanograms were decreased by glycerol ingestion from 126,4 +/- 107 daPa to 121,2 +/- 113 daPa but without any significant statistical difference. The resonance frequency was increased by glycerol ingestion from 905,88 +/- 145

to 954 + -130 Hz with a significant statistical difference (p<0.005). Glycerol test in healthy subjects, without any hydrops seems to have few effects on hearing. However, the inner ear fluid pressure can be decreased by glycerol even in healthy subjects as demonstrated by the resonance frequency increase. The next step of this study will be to assess the glycerol test associated to multifrequency admittancemetry in Meniere's Disease patients in order to predict the therapeutic effect of glycerol.



#### A COMPARISON OF ECOCHG. VEMP. VNG AND ROTARY CHAIR RESULTS IN PATIENTS DIAGNOSED WITH MENIERE'S DISEASE

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This study compares the results of 4 tests commonly used in the diagnosis of Meniere's Disease/endolymphatic hydrops (MD) from a group of patients with a confirmed diagnosis of this disorder to determine which test (or combination of tests) is the most sensitive and specific for this application. Data were gathered from the charts of 30 adults (16 male and 14 female) who had undergone Electrocochleography (ECochG), Video Nystagmography (VNG), Vestibular Evoked Myogenic Potential (VEMP) and Rotary Chair (RC) testing to help diagnose MD. Fisher exact test and chi-square analysis were used to examine the correlation between tests in determining the diagnosis of MD. Sensitivity and specificity were also calculated for each diagnostic test. Post-hoc analysis using Bonferroni correction chi-square on each pair of diagnostic tests revealed a statistically significant (p<0.01) difference between ECochG and RC, ECochG and VEMP, VNG and VEMP and VNG and RC. The overall sensitivity and specificity of each test were also calculated. Although the sample size was relatively small, the results are consistent with previous studies in that ECochG was the most sensitive and specific test for MD followed by VNG. The combination of ECochG and VNG showed a statistically significant difference between VEMP and RC in the diagnosis of MD.

#### ELECTROCOCHLEOGRAPHY AND VESTIBULAR EVOKED MYOGENIC POTENTIAL IN MENIERE'S DISEASE

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Introduction: as Meniere's Disease is a chronic inner ear dysfunction without any definite diagnostic tools, the goal of study was evaluation the results of electrocochleography (ECoG) and cervical vestibular evoked potential (cVEMP) tests in adult patients with definite Meniere's Disease and correlation of these both tests with each other.

Patients and Methods: 62 patients after excluding ones with previous history of otologic surgery or injections or neurologic disorders were enrolled. Click sound stimulation for ECoG and tone burst sound stimulation (500 Hz) for cVEMP test were used. Summation potential (SP) to action potential (AP) ratio more than 0.4 was accepted as elevated ECoG. In addition, absent wave, elevated threshold, or abnormal morphology was considered negative cVEMP test. All tests were done in non-active phase of disease according to clinical findings.

Results: 58% of patients were female and mean age of patients were 43.66 years old. Mean follow up in them were 46.8 months. 75% of patients had elevated ECoG and in whom that disease were on right side according to AAO-HNS guideline (29 patients), 79.3% had elevated results while in patients with left side clinical disease (27 patients), elevated ratio was 66.8%. The results for cVEMP test are as the following: 71% had negative cVEMP overall, while in 58.6% of patients with right sided disease and 77.3% of those with left sided disease, test results were negative. Pearson correlation coefficient of both tests were not statistically significant. No correlation between age or duration of disease and test results were seen.

Conclusion: as both tests had some beneficial helps for diagnosing Meniere's Disease, none of them cannot be used as a diagnostic modality. Combination of both tests for diagnosis may be helpful, as they did not had significant correlation.

### RETROSPECTIVE EVALUATION OF HYDROPS DIAGNOSTIC ON MENIERE'S DISEASE

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To evaluate the value of both electrocochleography and the glycerol test for the diagnosis of Menière's disease and the decision making for treatment.

128 patients with Menière's disease as diagnosed by medical history and clinical picture were examined with electrocochleography and the glycerol test. Results were classified is being hydrops positive or hydrops negative with respect to standard criteria. The decision for hydrops specific therapy (Acetazolamide therapy, sac decompression, nerve section) was based on the results of the examinations. The success of the therapy was rated as complete remission, partial remission or no success over a period of 3 months, 1 year and more than 1 year. The results were compared to that of a group with negative criteria for Menière's disease. The remission rate of any of these treatments was higher in the hydrops positive group compared to the hydrops negative group. The calculated sensitivity of the test is 0.71 for the electrocochleography and 0.65 for the glycerol test. The hydrops tests give some help in the decision making for therapy in Menière's disease. However, the low sensitivity rate might miss some patients with Menière's disease. The reasons for the low sensitivity and specificity are discussed.

# **VESTIBULAR DIAGNOSTICS**

### OCULAR AND CERVICAL VESTIBULAR-EVOKED MYOGENIC POTENTIALS TO AIR CONDUCTED SOUND AND BONE CONDUCTED VIBRATION IN MENIERE'S DISEASE

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Introduction. The changes which occur in the labyrinth during Meniere's Disease (MD), are still poorly understood. In this study we sought to test otolith function by using a relatively new technique in MD patients even during the acute MD attack. Air Conducted Sound (ACS) and Bone Conducted Vibration (BCV) delivered at the midline of the forehead at the hairline (Fz) (causing simultaneous and approximately equal amplitude linear acceleration stimulation at both mastoids) results in cervical evoked myogenic potentials (cVEMPs) recorded over contracted SCM and ocular evoked myogenic potentials (oVEMPs) recorded beneath both eyes while the subjects is looking up. Methods. 30 patients with definite Meniere's Disease during quiescence, meeting guidelines set by the AAO-HNS criteria, were tested at MSA ENT clinic in Cassino (Italy) with ACS (500, 750 and 1000 Hz) and Fz BCV 500 Hz oVEMPs and cVEMPs on two occasion. 13 subjects with definite Meniere's Disease were tested during quiescence and at the time of attack. 16 healthy control subjects were tested at comparable intervals in the same paradigm. Results. Responses to Fz BCV short tone burst stimuli confirmed results obtained by Manzari et al. 2010, showing significant asymmetry of n10 of the oVEMP to Fz BCV 500 Hz STB during the attack compared to guiescence but with no detectable change in the symmetry of the BCV cVEMP during the attack compared to quiescence. Healthy control subjects tested on two occasions showed no detectable change in the symmetry of oVEMPs or cVEMPs to Fz BCV 500 Hz STB. Responses to ACS showed different results. In patients during guiescence ACS cVEMPs and oVEMPs revealed different tuning or sometimes ACS cVEMPs potentials are present and ACS oVEMPs absent and viceversa . At the time of attack ACS cVEMPs in MD subjects show quite same results obtained with BCV while n10 to ACS oVEMPs in attack is enhanced. When applying tone bursts in normal, there is a frequency tuning with lowest thresholds at 500–1000 Hz and best responses at 500 Hz for cVEMPs in normals confirming Rauch et al. 2006. Air-conducted sound oVEMP exhibited a dominant peak located at 750 or 1000 confirming Lewis et al 2010.

Conclusion. In Meniere's Disease patients air conducted sound short tone burst stimuli showed not reliable results. These results are to signify that this stimulus in MD patients is not symmetrically delivered to the otolithic regions (utricular macula and saccular macula), probably due to the endolymphatic hydrops that hinders the arrival of the stimulus to these inner ear regions. In other words, a mechanical process rather than an ionic change in endolymph may be responsible for this vestibular potentials behavior in MD patients.



#### VESTIBULAR EVOKED MYOGENIC POTENTIALS IN MENIERE'S DISEASE

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This study was designed in order to clarify the changes in vestibular evoked myogenic potentials (VEMP) in Meniere's Disease. In addition, its role and feasibility as a test battery in diagnosis and follow-up of Meniere's Disease was also evaluated.

The study population included nineteen patients with Meniere's Disease (7 male, 12 female; mean age 46.15 years) and eighteen healthy volunteers (7 male, 11 female; mean age 32.44 years). P1 and N1 wave latency, P1-N1 latency difference, P1 and N1 wave amplitude and P1-N1 amplitude difference were obtained from two groups using 500 Hz, 1000 Hz and 2000 Hz tone burst stimuli. Statistical analysis was performed using the Mann-Whitney U test.

In the diseased ears of patients with Meniere's Disease, the P1 and N1 latency was elongated when compared to those obtained from healthy volunteers. The amplitude of P1 and N1 waves and the amplitude difference also decreased in all tested frequencies. However, this difference was statistically significant only in N1 amplitude and P1 latency of all frequencies tested.

The increase of P1 and N1 wave latency and decrease of both amplitudes are the two main changes in the VEMP of patients with Meniere's Disease. Vestibular evoked myogenic potential is an easy, fast and relatively inexpensive test for the evaluation of patients with Meniere's Disease.

## OCULAR (O-VEMP) AND CERVICAL (C-VEMP) VEMPS IN PATIENTS WITH "CLINICALLY CERTAIN" MENIERE'S DISEASE

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To compare c-VEMPS and o-VEMPS in patients with a certain diagnosis of Meniere's Disease and in controls to see if they could detect saccular hydrops.

Ethical approval was obtained. 22 control subjects and 17 subjects with "Clinically Certain" Meniere's Disease (AAOHNS criteria plus electrocochleographic confirmation of cochlear hydrops) were tested. Custom-written evoked potential averaging software on a laptop was used to evoke c-VEMPs and O-VEMPS. Interleaving stimuli at different intensities aided the accuracy of threshold detection. c-VEMP P1, N1 and P2 peaks and o-VEMP N1, P1, N2, P2, N3 and P3 peaks were analyzed with respect to amplitude, latency and threshold. Subjects were asked to indicate on a linear scale (difficult→easy) the degree of difficulty they experienced flexing the neck for c-VEMPS or gazing upward for o-VEMPS.

Threshold: There was no significant difference between Meniere's ears and controls for c-VEMPs or o-VEMPS. Amplitude: a significant reduction in c-VEMP P1N1 and N1P2 and in o-VEMP N2P2 amplitudes in Meniere's ears compared to controls. Latency: The c-VEMP N1 peak was significantly prolonged in Meniere's ears. For o-VEMPS no latency differences were found. The majority (67%) of participants would prefer having the o-VEMP test rather than the c-VEMP test.

This small study of VEMPS in "Clinically Certain" Meniere's Disease has produced some negative findings at variance with other studies in regard to threshold, but by amplitude measures both c-VEMPs and o-VEMPS can reliably detect saccular hydrops. Patients prefer the o-VEMP test.

# NORMAL VIDEO HEAD IMPULSE TEST WITH ABNORMAL CALORIC IRRIGATION TEST IN DEFINITE MENIERE'S DISEASE: A POTENTIAL **NEW CRITERIA FOR DIAGNOSIS?**

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Menière's Disease (MD) is currently diagnosed according to American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) criteria. The diagnosis of MD still remains difficult at early stage of the disease (possible lack of criteria as hearing loss or tinnitus). Using VHIT allows exploring the vestibule-ocular reflex (VOR) gain of the three semi-circular canals at physiological frequencies, offering more distinct data than caloric test. This work aimed at studying Video Head Impulse Test (VHIT) on patients affected by MD.

Study Design: prospective study in a tertiary referral center, of consecutively included patients with MD. Definite MD patients were included, according to AAO-HNS criteria. All patients had normal MRI excluding others inner ear diseases and sensorineural hearing loss had to involve low- and medium- frequencies. VHIT was performed as well as caloric testings under videonystagmoscopy (Synapsys<sup>®</sup>). Abnormality of caloric test was defined by unilateral deficit above 20%, while VHIT abnormality was defined by VOR gain value under 0.68 or presence of saccades. The main outcome measurement was the percentage of normal VHIT compared with that of normal caloric testings using Student t-test. Results: 37 patients were included, with a mean age of 56 years  $\pm$  12.7. Mean hearing loss was 59 dB HL  $\pm$  18.3. Twelve patients experienced Tumarkin's attacks. All patients had normal VHIT. Four patients (11%) had normal caloric tests and 33 (89%) patients had abnormal caloric tests with a mean unilateral deficit of 45%. The percentage of normal VHIT was significantly higher than that of normal caloric tests (p<0,05).

Conclusion: this study suggests that VHIT could be normal in patients with definite MD when applying a VOR gain value under 0.68. Further studies are required in order to confirm these results with a larger group of patients.

## INSTRUMENTAL ASSESSMENT IN MENIERE'S DISEASE: WHICH ROLE FOR VIDEO HEAD IMPULSE TEST?

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In patients affected by Menière's Disease (MD) a complete assessment of the peripheral vestibular function is mandatory, in order to provide a staging of the disease, to plan any kind of therapy and to get useful informations about the prognosis. Both caloric test (CT) and Video Head ImpulseTest (vHIT) represent a validated method to assess the function of the peripheral vestibular system by investigating the function of horizontal semicircular canal (HSC): since they test HSC responses respectively with low and high frequencies of stimulus, CT and vHIT are considered as complementary

The aim of the study was to analyze and compare vestibule-oculomotor reflex (VOR) features in 2 populations of MD patients, respectively treated or not treated with intratympanic gentamicin (ITG), employing CT and vHIT. Clinical and instrumental findings of 59 MD patients seen within a one year period in a tertiary referral center were retrospectively analyzed. The whole series was divided into two groups: group 1 was represented by patients treated with intratympanic gentamicin (ITG), while group 2 was made by patients treated with conservative medical therapy. Video Head Impulse Test finding were put in relationship with canal paresis (CP), hearing loss (pure tone average - PTA) and duration of MD. A statistical analysis was made in order to show any significancy (set at p=.050).

The high-frequency VOR gain was significantly reduced on the affected side in the group treated with ITG, where this asymmetry correlate with the degree of CP as well. No correlation was found in both groups between high-frequency VOR gain and the following: PTA and duration of MD

The study showed that high-frequency VOR is preserved even in the late stage of MD; the dissociation between CP and vHIT findings could represent an important instrumental hallmark of MD.





#### OCULAR VEMP FINDINGS IN PATIENTS WITH MENIERE'S DISEASE

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Vestibular-evoked myogenic potentials (VEMP) recorded from extra-ocular muscles, the so-called ocular VEMP (oVEMP), is becoming commonly used to evaluate the utricular vestibulo-ocular reflex (VOR) and superior vestibular nerve function. This study was designed to collect and evaluate normative data for oVEMP findings induced by air conducted sound stimuli in normal healthy subjects and compare this data with those obtained from patients with definite Meniere's Disease (MD). Thirteen male and 18 female patients, aged between 35-70 years (mean: 51.9±10.6) and 30 age matched healthy controls were enrolled in this study. Latencies and amplitudes of N1 and P1, peak-to-peak N1-P1 amplitude and asymmetry ratios (AR) at 95 dBnHL, 500 Hz air conducted tone burst stimulation level and wave thresholds of right and left sides were recorded in all normal participants and MD patients. The effects of gender on oVEMP results were also investigated. It was found that oVEMP wave thresholds and amplitudes were significantly different between healthy adults and patients with definite MD. However, there were no significant gender differences in terms of oVEMP parameters. oVEMP may be a valuable part of the diagnostic test battery for Menière's disease.

# IMAGING

### A REAPPRAISAL OF MENIERE'S DISEASE SUPPORTED BY VARIABLE LATENCY OF SYMPTOMS AND MRI VISUALIZATION OF THE ENDOLYMPHATIC HYDROPS

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Menière's disorder is a symptom complex comprising attacks of vertigo, hearing loss and tinnitus which are associated with endolymphatic hydrops (EH) of the inner ear. Medical practitioners often have difficulty making the diagnosis due to the heterogeneity of the symptoms. With modern imaging techniques the visualization of the EH has become possible in, and the disorder seems to be more common and complex than hitherto believed.

We assessed the symptom entity of 340 patients entering a tertiary hospital and the occurrence of the clinical symptoms among 740 patients belonging to a Menière association. We used 3T MRI to image EH in the inner ear with gadolinium contrast agent (either transtympanic or intravenously administered GdC) among 224 patients.

In onset of the first symptoms only 38 % of the patients had the symptom triad at clinical entry, permitting a clinical diagnosis of a definite Menière's disorder. The mean age of onset of first symptom was 43.8 years, with about 10 % of the patients being older than 65 years. The time delay between hearing loss and vertigo was more than five years in 20 % of the patients. Gadolinium contrasted MRI demonstrated EH in EH was present in 190 out of 205 ears (93%) with symptoms attributable to Menière's disorder (both transtympanic and intravenously administered GdC). The vestibule showed EH more frequently than did the cochlea (p<0.004). In patients with unilateral symptoms 75 % the EH was bilateral. Patients with a single inner ear symptom such as vertigo, fluctuant hearing loss, or tinnitus comprised a heterogeneous group on MRI findings. 53 % of patients with sudden hearing loss showed EH. 69 to 95% of the other patient groups had EH. The EH was more frequently observed in the vestibule than in the cochlea (p=0.025). Menière's disease shows often bilateral EH and comprises a continuum from a mono-symptomatic disease to the typical symptom complex of Menière's disorder. We suggest that a 3T-MRI measurement should be carried out in patients with sensorineural hearing loss, vertigo, and tinnitus either transtympanically 24 h after injection or 4 h after intravenous injection of GdC to verify the inner ear pathology. The terms vestibular Menière's disorder or cochlear Menière's disorder should be used in mono-symptomatic patients. This can lead to better management of the condition.

# ENDOLYMPHATIC HYDROPS IN PATIENTS WITH UNILATERAL AND BILATERAL MENIERE'S DISEASE

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To evaluate the endolymphatic space size on both sides in patients with unilateral and bilateral Meniere's Disease (MD), and to investigate the factors contributing to progression to bilateral MD with respect to the development of endolymphatic hydrops (EH). Retrospective review of medical records at an academic university hospital. The subjects for this investigation included 29 patients with definite unilateral MD, and 12 patients with definite bilateral MD, according to the criteria established by the American Academy of Otolaryngology-Head and Neck Surgery in 1995. The endolymphatic space size was visualized 4 hours after intravenous gadolinium administration and/or 24 hours after intratympanic gadolinium injection using 3-Tesla magnetic resonance imaging. A radiologist blinded to the patient's clinical data classified the degree of EH in the vestibule and the cochlea into 3 groups: none, mild, or significant. In the 29 ears with unilateral MD, some degree of EH was observed in either the cochlea or the vestibule. Significant EH was observed in the cochlea and in the vestibule in 24 and 20 ears, respectively. On the non-affected side, significant EH was observed in the cochlea and the vestibule in 4 and 6 ears, respectively. Neither the cochlea nor the vestibule showed EH in 8 of the 29 ears on the non-affected side. In the 12 patients with bilateral MD, significant EH was observed in all the patients either in the cochlea or in the vestibule.

In all 53 ears with definite MD, some degree of EH was observed either in the cochlea or in the vestibule. The use of MRI may provide useful information regarding progression from unilateral MD to bilateral MD.

# MRI EVALUATION OF ENDOLYMPHATIC HYDROPS AND CLINICAL APPLICATION FOR SURGICAL MANAGEMENT

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Visualization of endolymphatic hydrops (EH) has recently become possible using MRI with contrast agents. The relationship between EH on MRI and otological examinations in patients with Meniere's Disease has been investigated, and it was found that physiological function was related not only to the degree of EH, but also to the persistence of EH. EH could be found in cases of candidates for middle ear surgery, such as otosclerosis, and preoperative EH could be a risk factor for inner ear disturbances following surgery. We investigated the presence of EH on MRI in ears with clinical otosclerosis, and further studied to compare preoperative MRI findings and postoperative symptoms following stapes surgery to evaluate the efficacy of such MRI evaluation for the management of ears with otosclerosis. Subjects diagnosed as having otosclerosis and agreed to MRI examination were randomly recruited in the study. Ears were evaluated by MRI performed 4 h after intravenous injection of gadolinium. The degree of EH in the vestibule and cochlea was classified into three grades (none, mild, and significant). Imaging data were compared with clinical findings. In ears operated, imaging data concerning the degree of EH were compared with postoperative clinical findings.

Varying degrees of cochlear EH and vestibular EH were observed. Episodes of acute sensorineural hearing loss with rotatory vertigo occurred in some ears that showed severe EH in the cochleae and vestibules. Severe EH, however, was also observed in ears without such symptoms. The postoperative course in all ears with no EH in the vestibule was uneventful, with successful improvement of hearing levels, but a case with severe EH in the vestibule had postoperative nystagmus and long period of dizziness. The presence of EH in ears with otosclerosis was clearly visualized in the present patient series. Moreover, the presence of EH in the vestibule on MRI might be a high risk factor in ears that are candidates for stapes surgery. Such MRI evaluation could provide useful information for managing symptoms related to EH.



# MRI IMAGING OF INNER EAR ENDO-PERILYMPHATIC SPACES AT 3 TESLA AFTER INTRATYMPANIC CONTRAST AGENT ADMINISTRATION IN DEFINITE MENIERE'S DISEASE

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MRI findings in Meniere's Disease are not yet defined. The purpose of this study was to determine the main findings of endoperilymphatic spaces in patients affected by Definite Meniere's Disease using Magnetic Resonance Imaging (MRI) with intratympanic administration of contrast agent.

Twenty-two patients with Definite Meniere's Disease underwent 3 Tesla MRI. 3D FLAIR and 3D T2 SE sequences were acquired 24 hours after intratympanic administration of 0.4-0.5 ml of gadobutrol diluted eightfold with saline. Contrast agent was injected through the tympanic membrane with a 25 G needle. Multi Planar Reconstructed (MPR) images were analyzed. According to literature, vestibular endolymphatic hydrops was graded considering the ratio of the area of the endolymphatic space to the vestibular fluid space (sum of the endolymphatic space and perilymphatic space). Patients with no hydrops had a ratio of one third or less, those with mild hydrops had between one-third and a half and those with severe hydrops had a ratio of more than 50%. Cochlear and semicircular canals endolymphatic hydrops was defined as positive when a MRI signal void was detected.

No adverse events due to contrast agent administration were observed. Four patients didn't show perilymphatic enhancement thereby they were not considered for data analysis. Vestibular endolymphatic hydrops was observed in 89% of patients and it was severe in 10 out of 16 patients.

Whereas posterior semicircular canal endolymphatic hydrops was observed only in

5 out of 18 patients (28%); lateral and superior semicircular canals endolymphatic hydrops was observed only in 7 out of 18 patients (39%); cochlear endolymphatic hydrops was observed only in 9 out of 18 patients (50%).

Our study confirms that endolymphatic hydrops can be detected at 3T MR images after intratympanic contrast agent administration and is the main finding in patients with Definite Meniere's Disease.

Moreover, our preliminary results seem to suggest that endolymphatic hydrops may affect more often the vestibule than cochlea or semicircular canals.

#### MRI INNER EAR IMAGING AND TONE BURST ELECTROCOCHLEOGRAPHY IN THE DIAGNOSIS OF MENIERE'S DISEASE

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To compare the sensitivity of Gadolinium MRI inner imaging with tone burst electrocochleography (EcochG) for diagnosing endolymphatic hydrops.

Study Design: A prospective study on patients who were to have an MRI scan to exclude retrocochlear pathology. Setting: Tertiary care centre.

Patients: 102: 57 patients with Possible, Probable or Definite Meniere's Disease, 25 with asymmetrical hearing loss, 18 with sudden sensorineural hearing loss and 2 with unilateral tinnitus had additional MRI inner ear imaging and click and tone burst stimulus EcochG testing.

Intervention: Diagnostic.

Main Outcome Measure: To compare the sensitivity of the two techniques.

In 30 patients with symptom-based Definite Meniere's Disease tone burst EcochG was positive in 25 (83%) and the click EcochG was positive in 9/30 (30%), and Gadolinium MRI imaging diagnosed hydrops in 14 (47%). A positive result for either MRI imaging or tone burst EcochG was seen in 26 patients (87%). In 14 subjects with symptom-based Probable Meniere's Disease 10 (71%) had either a positive EcochG or MRI. In 13 with Possible Meniere's Disease, 4 (31%) had a positive EcochG or MRI.

This study confirms the greatly enhanced diagnostic sensitivity of tone burst EcochG over click response in diagnosing endolymphatic hydrops in Meniere's Disease. Even though adequate MRI imaging was achieved in 90%, tone burst EcochG was a more sensitive test.

# IMAGING OF ENDOLYMPHATIC SPACE IN PATIENTS WITH MENIERE'S DISEASE AND NON-OTOLOGICAL DISEASES

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To explore the endolymphatic hydrops (EH) with magnetic resonance imaging (MRI) in Meniere's Disease (MD) and healthy ears. We studied 307 Patients (412 ears) with Meniere's Disease patients and 18 (36 ears) patients with healthy ear patients who have other benign disease non-associated with hearing or vestibular function in our hospital. The mean ages of the subjects were 52.9 years (range 13 to 86 years) in MD group and 55.9 years (range 24 to 79 years) in the healthy group. MRI was performed 24 hours after intratympanic injection of qadolinium or 4 hours after intravenous gadolinium administration. EH in cochlea were present in 302 out of 407 MD ears (74.2%) and 14 out of 34 healthy ears (41.2%). Significant cochlear hydrops was present 217 out of 407 MD ears (53.3%) and 4 out of 34 healthy ears (11.8%). EH in the vestibule was present in 345 out of 406 MD ears (85.0%) and 3 out of 34 healthy ears (9.0%). Significant vestibular hydrops was present 235 out of 406 MD ears (57.9%) and none of 34 healthy ears (0%), respectively.

All of definite MD patients had EH in the cochlea or vestibule in our study. There were little bilateral differences of cochlear EH. The main cause of the high rate of cochlear EH was that our criteria assessed the largest EH in the cochlea. Further study is needed for silent cochlear EH may contribute to the pathogenesis of MD or not. On the other hand, vestibular EHs with healthy ears were obviously lesser than with disease ears, this showed strong association with inner ear symptoms or disease.

#### UNDERSTANDING MENIERE'S DISEASE: THE CONTRIBUTION OF HYDROPS- MRI

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Meniere's Disease (MD) is an intractable, debilitating disease which has not been fully understood in terms of its causes and pathophysiology. Though endolymphatic hydrops (EH) has been thought to be the pathological explanation of MD, there is no test for definite diagnosis or accurate prognosis. We have reviewed the latest research findings on how EH Magnetic imaging (MRI) has contributed to more accurate diagnosis and improved pathophysiological understanding and may have an impact on the choice of appropriate treatment of MD. After inner ear 3T-MRI made it possible to delineate EH in patients with MD following intratympanic gadolinium-based contrast media (GBCM) administration (IT-Gd) in 2007, numerous studies have tried to visualize EH by using different routes of GBCM. Subsequently IT-Gd and intravenous GBCM administration (IV-Gd) have been varied with different sequences, such as three dimensional fluid attenuated inversion recovery (3D-FLAIR), heavily T2-weighted 3D-FLAIR, and 3D-IR sequences to accurately visualize EH. More recently, there have been rigorous investigations in the area including assessment of the size and location of EH, and the relation of the degree of EH to clinical symptoms and audiovestibular function tests, such as pure tone audiometry, Electrocochleography, Vestibular-evoked myogenic potential (VEMP) and Caloric tests. These analyses of the relation between EH and clinical findings contribute to differentiate MD from other diseases with similar presentations, such as vestibular migraine and peripheral recurrent vertigo. The accurate identification of MD with MRI will lead to better management of the condition.



#### ENDOLYMPHATIC SPACE SIZE IN PATIENTS WITH VESTIBULAR MIGRAINE AND MENIERE'S DISEASE

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Meniere's Disease (MD) is characterized by episodic vertigo, fluctuating hearing loss and tinnitus. Vestibular migraine (VM) is a relatively new disorder that is characterized by episodic vertigo or dizziness, coexisting migraine and shortage of hearing loss. It is occasionally difficult to distinguish between VM and vestibular MD with headache. Because endolymphatic hydrops (EH) is a characteristic sign of MD, we attempted to evaluate endolymphatic space size in both diseases. Endolymphatic space size in the vestibule and the cochlea was evaluated in seven patients with VM and age- and sex-matched 7 patients with vestibular MD. For visualization of endolymphatic space, three-tesla magnetic resonance imaging (3T MRI) was taken 4 hours after intravenous injection of gadolinium contrast agents using three-dimensional fluid attenuated inversion recovery (3D FLAIR) and HYDROPS (HYbriD of Reversed image Of Positive endolymph signal and native image of positive perilymph Signal) techniques. In the vestibule of VM patients, EH was not observed except for two patients with unilateral or bilateral EH. On the contrary, in the vestibule of patients with vestibular MD, all patients had significant EH bilaterally or unilaterally. These results indicated that endolymphatic space size is significantly different between VM and vestibular MD.

# SYMPOSIUM "INTRATYMPANIC DEXAMETHASONE AS A TREATMENT FOR MENIERE'S DISEASE"

#### INTRATYMPANIC DEXAMETHASONE AS A TREATMENT FOR MENIERE'S DISEASE

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The use of intratympanic steroids for the management of patients with Meniere's Disease has gained popularity over the last decade as a safe and effective, non-destructive method to address these patients' symptoms. In view of the increasing evidence available from clinical trials, this presentation will present an update of the currently available evidence from high quality randomized clinical trials.

# PERILYMPH PHARMACOKINETICS OF GLUCOCORTICOSTEROIDS AFTER INTRATYMPANIC. INTRACOCHLEAR, AND INTRALABYRINTHINE DELIVERY

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Glucocorticosteroids are the most commonly applied drugs for the treatment of inner ear disease. Rational pharmacotherapy of the inner ear requires an understanding of pharmacokinetics according the LADME principles: liberation, adsorption, distribution, metabolism and elimination. A number of studies have investigated the pharmacokinetics of glucocorticosteroids in the inner ear using different drug delivery strategies and systems. The knowledge gained from these studies is reviewed in this presentation, and includes the following findings:

Intratympanic (extracochlear) applications lead to higher intracochlear perilymph concentrations than with systemic application. The intracochlear concentrations after round window application, are highly variable, and are related to the time the drug is in contact with the round window. Thus, perilymph drug concentrations depend on the delivery system used. In addition, a fast elimination from the cochlear fluids and the very low perilymph flow rate result in substantial basal-apical concentration gradients. Elimination occurs more rapidly from scala tympani (ST) than from scala vestibuli (SV). Elimination half-times for dexamethasone have been estimated with 22.5 min for ST and 111 min for SV, respectively. If the variability in peak concentration and gradient is also present under clinical conditions, this may contribute to the heterogeneity of outcome that is observed after intratympanic application of alucocorticoids for various inner ear diseases.

Animal studies show that intracochlear applications have advantages over intratympanic injections with significantly higher, less variable drug levels and smaller base-to-apex concentration gradients. For further development of this technique, however, it is of importance to control leaks of perilymph and drug from the injection site and to evaluate its clinical feasibility and associated risks. Initial results of sealing techniques have been successfully tested for other substances. The prodrug dexamethasone phosphate is metabolized to the active moiety dexamethasone base. The metabolic pathways, however, that degrade dexamethasone in the liver (by hydroxalases CYP3A4 and CYP17) do not contribute to the rapid elimination of Dex from perilymph.

Recent experiments found that dexamethasone may decrease endolymph volume or slow the rate of CSF influx that occurs in the normal cochlea, and thus influence fluid physiology in the intact ear.

# RESULTS FROM A PHASE 2B CLINICAL TRIAL TO ASSESS THE SAFETY AND EFFICACY OF EXTENDED-RELEASE DEXAMETHASONE THERMOSENSITIVE GEL FOR INTRATYMPANIC ADMINISTRATION IN SUBJECTS WITH MENIERE'S DISEASE

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IV steroid solutions are routinely injected intratympanically (IT) as off-label treatment for Meniere's Disease (MD), however they provide limited cochlear exposure necessitating repeat injections. OTO-104 is a novel formulation of 6% dexamethasone in thermosensitive gel that has been developed to overcome these limitations. We therefore investigated the safety and efficacy of a single IT injection of OTO-104 in MD subjects. A previous Phase 1b study demonstrated that OTO-104 reduced vertigo frequency and tinnitus handicap after a single IT injection compared to placebo.

Prospective, randomized, double-blind, placebo-controlled, Phase 2b clinical trial evaluating 140 unilateral MD subjects, ages 18 to 85 years. Subjects entered a 1-month baseline period to characterize disease status, followed by a 1:1 randomization to OTO-104 (12mg) or placebo. Subjects were monitored for 4 months following injection. The primary endpoint of the trial was the reduction in vertigo frequency during Month 3 compared to baseline. Safety was assessed with otoscopy, audiometry and tympanometry. A total of 154 subjects were enrolled in the study. Baseline data show that the study patient population in this Phase 2b study was comparable to the MD population assessed in the previous Phase 1b study. OTO-104 demonstrated a 61% reduction from baseline in vertigo frequency in Month 3 vs. 43% for placebo (p=0.067), which narrowly missed achieving statistical significance. Statistical significance was achieved on several prospectively defined secondary vertigo endpoints. The clear efficacy trends in vertigo observed in this trial provide a basis to advance OTO-104 to Phase 3 testing as a potential novel therapeutic to treat Meniere's Disease.





# DIAGNOSTICS

## EFFECTS OF BODY TILT ON MULTIFREQUENCY ADMITTANCE TYMPANOMETRY

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Hydrops and abnormalities of inner fluid pressure are involved in some otologic diseases such as Meniere's Disease (MD). However, demonstrating abnormal perilymphatic or endolymphatic pressure is challenging. Multifrequency tympanometry studies in MD patients demonstrated an increase of the width of conductance tympanograms (outside an attack) compared with controls. To confirm that the increase in conductance width is caused by hyperpressure and not hypopressure in these patients tested outside an attack, we assessed the effect of changes in inner ear fluid pressure caused by body tilt on the results of multifrequency admittancemetry tympanograms.

A multifrequency tympanometry including conductance (G) tympanogram at 2 kHz and resonance frequency measurements were performed in 20 volunteers (40 ears) free of otologic or neurologic disease. The measures were collected in three different positions: vertical, supine, and Trendelenburg positions.

Changes in inner ear fluid pressure caused by body tilt induced an increase in the width of G tympanograms. In the vertical position, the mean value was 141.7 + 56.5 daPa; in the supine position, it increased to 158 + 58.3 daPa; and increased even more in the Trendelenburg position (20 degrees), with a mean of  $184 \pm 69.6$  daPa (p < 0.01). Resonance frequency also increased in the Trendelenburg position. We conclude that the increased width of G tympanograms in MD patients outside an attack may be caused by an increase in inner ear fluid pressure.

#### PREDICTIVE VALUE OF ECOCHG IN OFFSPRING/SIBLINGS OF INDIVIDUALS WITH MENIERE'S DISEASE

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The use of Electrocochleography (ECochG) in the identification, assessment and management of Meniere's Disease/endolymphatic hydrops (MD) is well documented in the literature. The current study was designed to assess whether ECochG might also be valuable as a screening tool to help predict this disorder in individuals who may be genetically predisposed to developing it. To date, ECochG has been recorded from a small sample (9) of subjects with no history/symptoms of MD, but who are either the offspring or siblings of individuals with a confirmed diagnosis. Seven of these subjects had positive electrocochleograms for MD, a percentage that is considerably higher than the incidence of false positive results we have found in the general, non-MD population. These results have motivated us to continue this line of research with the following guestions in mind: is there time prior to the onset of symptoms that the initiation of MD may be detected and, if so, can interventional approaches (e.g., lifestyle/dietary changes, pharmaceutical intervention, allergy control) be implemented to help prevent/delay the onset of symptoms.

# CLINICAL APPLICATION OF THE THRESHOLD EQUALIZING NOISE TEST IN PATIENTS WITH MENIERE'S DISEASE: A PRELIMINARY STUDY

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Cochlear dead regions (DRs) are defined as areas of inner hair cells and/or related neurons, which may not function normally in hearing loss at a given frequency. The threshold-equalizing noise (TEN) test is designed to detect conveniently the presence of DRs in clinical settings. We aimed to make a preliminary assessment of the prevalence of cochlear dead regions in Meniere's Disease and relation between cochlear dead regions and hearing recovery. Between November 2010 and May 2015, 61 patients (65 ears) with Meniere's Disease who visited our outpatient clinic were prospectively enrolled. Pure tone audiometry and TEN (HL) test were performed for all the patients. DR at each frequency was indicated by masked thresholds of  $\geq$ 10dB above the TEN level and 10 $\geq$  dB above the absolute threshold. DR was present in 14% (n=9) of the 65 ears. According to audiometric configurations, DR was most common in moderately severe, flat hearing loss. The prevalence of DR was lower than that of SSNHL (sudden sensorineural hearing loss) in the previous study (the prevalence of DR in SSNHL: 26.5%). Mean hearing level was worse in the presence of DR (61.2±9.7dB) compared with that in the absence of DR (56.7±11.0dB). Word recognition score also worse in the presence of DR (47.6±31.6) compared with that in the absence of DR (67.9+25.3). DRs in Meniere's Disease were mainly distributed in the frequencies of 1k and 1.5k Hz. Among the presence of DR group, three patients had hearing recovery, two patients had hearing aggravation, and three patients had no chance of hearing. Most patients participated TEN test more than one year after sudden hearing loss, it was difficult to show the relation between hearing outcome and the presence of DR. Although performance of the TEN test was limited to show the relation with hearing prognosis in this study, the presence of DR showed poor result of hearing compared with the absence of DR. The prevalence of DR was different according to causes and TEN test may have the potential to be used as a prognostic tool for hearing loss.

# USE OF MULTIFREQUENCY ADMITTANCEMETRY ASSOCIATED TO GLYCEROL TEST TO ASSESS HYDROPS - NORMATIVE VALUES IN HEALTHY SUBJECTS

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Hypothesis: administration of a pulsatile pressure to the inner ear via a ventilation tube (basis of Meniett therapy) is able to effectively change the symptoms in patients with Meniere's Disease and this can be objectively evaluated measuring the endolymphatic hydrops (EH) through an electrochocleography (ECochG).

Background: Meniett therapy has been advocated by many as an effective tool in the staircase of treatments available for patients affected by Meniere's Disease, after the pharmacological therapy and before destructive treatments. Our study aims to evaluate the effects that micropressure treatment has on endolymphatic hydrops via the SP/AP ratio obtained through a transtympanic ECochG. Furthermore, we compared the results with the effects that the treatments had on the subjective symptoms of each patient. Methods: A total of 11 definite MD patients underwent micropressure treatment in our department from September 2014 to August 2015, following the inclusion criteria of:

- 1. Unilateral definite MD according to the AAO-HNS guidelines (2015),
- 3. No CNS symptoms.

ECochG and DHI were obtained from each patient 1 month before and 1, 3 and 6 months after administration of micropressure treatment. Values of SP/AP ratio greater than 0.48 were considered hydropic. **Results:** All selected patients were found to be hydropic (SP/AP ratio > 0.48) before the treatment started. EcochG after 1 month revealed EH in 72.7%, after 3 months in 18.2% and after 6 months in 18.2% of patients. Mean DHI was 83.36 at baseline, 47.18 at 1 month, 28.27 at 3 months and 26.27 at 6 months.

**Conclusion:** Although patients had an immediate relief from their symptoms after administration of micropressure treatment, most of them were still hydropic at 1 month. However, Meniett therapy not only succeeded in eliminating patients' symptoms at 3 months, but it was also effective on EH on more than 80% of them; these results remained stable after six months. Patients who after six months still suffered from hydrops, without improvement of symptoms, were addressed to vestibular neurectomy. Micropressure treatment is a refined therapy for MD and can obviate the need for surgery.

2. Recurrent and invalidating vertigo attacks not responding to diet modifications or pharmacological therapy for at least 1 year,





#### THE INTERACTIVE GPS SYSTEM FOR DIAGNOSIS OF VERTIGO

A. Belal Alexandria, Egypt

To save physician's time and patient's money, a road map for diagnosis of vertigo based on patient's history was introduced in 2005. Five questions leads to 10 destinations, 4 with ante vertigo and 6 with chronic dizziness. Each destination has an anatomical and etiological diagnosis that requires a specific set of tests and investigations. The road map was put into an interactive GP5 software program that puts the physician or patient in the driver seat, diagnosing vertigo while driving along the dizziness highway. Each exit leads him into the diagnostic building to do a specific set of tests, that will eventually take him to his final destination (diagnosis).

#### PREVALENCE AND FEATURES OF INFERIOR VESTIBULAR NEURITIS

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Vestibular neuritis (VN) is an acute unilateral vestibulopathy that commonly affects the superior vestibular nerve. The video head impulse test (VHIT) can help to diagnose inferior vestibular neuritis (IVN) by showing an isolated deficit on the posterior semicircular canal (SCC). The aim of this study was to evaluate the prevalence of IVN when managing acute vertigo, which could be higher when using VHIT in emergency.

From 2010 to 2013, a prospective study was conducted in a tertiary referral center for all consecutive adult patients admitted for a first vestibular syndrome mimicking VN with abnormal VHIT. IVN was diagnosed by isolated posterior SCC deficit on VHIT, normal caloric tests and torsional down-beating nystagmus.

Among the 46 patients, VN was considered to be IVN for 14 patients (30%), superior VN for 24 (52%) patients and both for 8 patients (18%). Caloric tests were normal for all patients with IVN whereas they were always abnormal when involving the superior vestibular nerve. None of them had neurological or cochlear disorder and MRI was normal for all patients.

This study confirmed the importance of VHIT when managing acute vertigo in order to differentiate central and peripheral disorder and to diagnose inferior VN.

#### THE SHORT FORM OF THE DIZZINESS HANDICAP INVENTORY: IS IT COMPARABLE WITH THE ORIGINAL ONE?

F. N. Ardıç, F. Tümkaya

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The dizziness handicap inventory (DHI) is a useful tool for reporting the patients' situation before and after the interventions. But there are so many questionaries' used in clinical practice like Vertigo Symptom Scale, Symptom Checklist-90, etc. The number of the questions is becoming more important for efficient working in the departments. Original DHI that proposed by Jacobson et al. in 1990 has 25 questions, while the short form (sDHI) proposed by Tesio et al. has only 13 questions. Our aim is to measure the correlation between two forms of DHI. The forms filled by 2111 dizziness patients were evaluated for this purpose. The DHI has 3 subscales. Patients answer the questions as no (0), sometimes (2) and yes (4). The sDHI has 2 subscales and patients replies only as no (0) or yes (1). Both of them show the degree of handicap according the total points. Although they have some correlation in subscales but they show the different aspects of the patient. One must be careful while comparing the results of the two scales.

# **ENDOLYMPHATIC HYDROPS**

## HORMONAL REGULATION OF POTASSIUM IN INNER EAR, A NEW EXPLANATION IN MENIÈRE'S CRISIS

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Menière's disease is an invalidating disease evolving by crisis, frequently triggered by stress and associating vertigo, deafness and tinnitus. Horner et al have reported that the plasmatic concentration of epinephrine higher in patient with a Menière's disease. In the inner ear, beta-adrenergic receptors are present in the endolymph secretory structures, as in the dark cells in vestibule. Ferrary et al have reported also that potassium concentration is decreased in the endolymph in an animal model of Menière's disease. These data suggest that catecholamine could be implicated in the potassium dysregulation in inner ear that conduct to Menière's disease crisis. The aim of this work is to study the role of catecholamine in potassium regulation and the role GJA1 in potassium transport in inner ear. We developed an immortalized vestibular dark cell line, EC5v, in the laboratory. This cell line allows us to study endolymph secretion under different type of stimuli, especially hormonal stimuli. The cells were cultured on filter to study the potassium transport using Rubidium. We used the real time PCR to explore the regulation of expression of GJA1 genes. Then we characterized proteins expression and localization using western blot and immunohistochemistry. In EC5v, potassium secretion, from basolateral to apical compartments, was clearly increased by 2-fold upon isoproterenol stimulation. The GJA1 gene expression was down regulate in EC5v by 2-fold upon isoproterenol stimulation. This effect is inhibited by the beat-receptor antagonism, propranolol. The connexin 43 (GJA1 gene) is down regulating upon isoproterenol and is localized in secretory region of the inner ear. Cardiac muscle and blodd-brain barrier epithelium studies reported a role in epithelial barrier of the connexin 43. The catecholamine increased during menière's crisis that could conduct to leakage in the peri-endolymphatic barrier and the movement of potassium through endolymph to perilymph along the ionic gradient.

# IMAGING FLUID DYNAMICS IN THE HYDROPIC EAR WITH LIGHT SHEET FLUORESCENCE MICROSCOPY

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Aim: To visualize dynamic endolymph flow in experimental hydrops in guinea pigs using Light Sheet Fluorescence Microscopy (LSFM). A clear understanding of fluid dynamics in the inner ear is vital to our understanding of Meniere's Disease, and may enhance our knowledge of inner ear pharmacokinetics. Techniques for investigating inner ear fluid dynamics include in vivo micropipette recordings of biomarkers, or imaging their distribution in histological slices or MRI scans. However, we still lack a clear understanding of the transport of endolymph, antigen, or drugs within the inner ear. We combined the use of 200 kD fluorescein isothiocyanate (FITC)-dextran perfusions with LSFM, to provide 3D images that provide insight into inner ear fluid dynamics. Via a glass micropipette, FITC-dextran in artificial endolymph was injected into scala media in anaesthetized guinea pigs. Measurements of cochlear and vestibular evoked-response thresholds were obtained continuously throughout the injection. Temporal bones were harvested, fixed in 4% PFA, decalcified, dehydrated in graded tetrahydrofuran, and immersed in dibenzyl ether to optically clear the tissue. Temporal bones were then imaged on our custom-built LSFM. A substantial amount of the FITC-dextran appears to be transported into the endolymphatic sac shortly after it has been injected into scala media. Moderate levels of FITC-dextran appear in the utricle and semicircular canals, but not in the perilymphatic compartments, suggesting that the membranous labyrinth remains intact, and that the FITC-dextran is able to pass through the utriculo-saccular duct. Whilst this technique requires termination, fixation, and optical clearing, and can thus only provide a 'snap-shot' of fluid dynamics, it provides highresolution 3D images of biomarker distribution, and offers the ability to modify the fluorescent biomarker to examine either intra- or intercompartmental fluid dynamics or pharmacokinetics. The remarkable uptake of FITC-dextran into the endolymphatic sac within 20 minutes supports the theory that the sac actively absorbs endolymph during hydrops. The presence of FITC-dextran in the pars superior, but not the perilymph, following sufficient endolymph injection to induce a sudden relief of a cochlear sensitivity loss, supports theories that the utriculo-saccular duct may open suddenly in the presence of severe endolymphatic hydrops.



<sup>7th</sup> International Symposium on Meniere's Disease and Inner Ear Disorders



#### MENIERE'S SYMPTOMS AND ENDOLYMPHATIC HYDROPS

C. A. Oliveira, MD, PhD Brasília University Medical School

Since the description of endolymphatic hydrops by Hallpike and Cairns all the physiopathology of Menière's symptoms was based on the assumption that the pathologicl lesion was the cause of the symptoms. Schuknecht came out with the theory of membranous rupture causing the mixing up of endo and perilymph leading to the appearence of Menière's symptoms. Lawrence had proved that this event caused destruction of hair cells and hearing loss in experimental animals. In 1989 I studied 89 temporal bones from the Massachusetts Eye and Ear Infirmary collection who were collected from patients with significant tinnitus during life. The goal was to find a pathologic correlate for tinnitus. Most of these bones had no findings in the temporal bone but the next most frequent anomaly among them was endolymphatic hydrops. The third was otosclerosis. Further more one third of the bones with normnal histopathology came from patients who also had vertigo during life. The idea of a continuum from normal bones to endolymphatic hydrops was attractive. But that would mean that Menière's symptoms could exist without hydrops and vice-versa. At this point endolymphatic hydrops must be thought of as an epiphenomenon that has a common preceding cause with the symptoms. The clear association of Menière's syndrome and migraine makes it possible that a central phenomenon starts the whole process. Certainly at least an attractive direction for future research.

#### ARE THERE NO NEWS ABOUT THE COCHLEAR HYDROPS?

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The endolymphatic hydrops (ELH) was first described by Yamakawa in1938 6 months before Hallpike and Cairns brought out their observation. Today, immunohistochemical investigations of the guinea pig cochlea, using specific antibodies to all 3 known NOS isoforms, particularly the inducible isoform of NO-synthase (iNOS/NOS II), the target enzyme soluble guanylyl cyclase (sGC) and the second messenger cGMP have been performed 1-4 weeks after closure of the right endolymphatic duct in guinea pigs. A continuous threshold shift was measured by BERA with a maximum of 30 dB in the 4th week.

Endolymphatic hydrops, the morphological substrate of Menière's disease, became histomorphologically evident by excavation of the Reissner's membrane in the paraffin sections of the cochlea. NOS II-expression could be noted in endothelium, spiral ganglion cells, in nerve fibers, in supporting cells of the Corti-organ and cells of the spiral ligament slightly one week after the surgical procedure. A strong increase was noted in the second and 3rd week, while immunoreactivity (NOS II) seemed to be declined 4 week after the surgical procedure. NOS I was expressed in the same pattern as in the untreated controls, whereas NOS III, sGC and cGMP showed a marked reduction in the second week and later compared to the control animals. Active caspase-3 could regularly be detected in SGC and was also frequently found in lateral wall.

We conclude that NOS II-generated NO could be involved in the pathophysiology of cochlear dysfunction in Menière's disease or other inner ear disorders with hydrops. The reduced expression of NOS III, sGC and cGMP could be seen as depletion but also as a counter-regulation. The activation of caspase-3 in SGC gives further evidence that radicals such as RNS or ROS could be involved in the early stages of ELH. RNS and ROS might induce apoptosis and cause the irreversible hearing loss in later stages of Menière's disease.

#### ANTERIOR MEMBRANOUS LABIRYNTH HYDROPS

#### S. Ferrara, F. Martines, P. Ferrara

Hydrops is the increase of fluids in the inner ear. A retrospective study included 12 patients (8 Females and 4 Maless) from March 2013 to March 2015. The study group had a median age of 47,5 (range 38-57 yr.). The patients were submitted to full otorhinolaryngological exam and audiometric evaluation. Patients showed an unilateral moderate conductive hearing loss for low frequencies or mixed hearing loss without vertigo. Transient unilateral fullness, tinnitus, recruitment and normal otoscopy. The aim of this study was to find out pathogenesis of this disease. Differential diagnosis was put with otosclerosis, otitis media, Meniere's Disease, transitory hearing loss and Lermoyez syndrome. More etiopathogenetic factors support hydrops: hydric metabolism theory, hormonal theory, hystamine theory and neurovegetative theory. Pathogenesis of anterior membranous labirynth hydrops is double: 1) increased production of endolymphatic fluids; 2) obstruction of endolymphatic duct or disfunction of endolymphatic sac. The patients were treated with diuretic, betamethasone, citicoline, cinnarizine, diet without salt, greasy and allergic foods. The right diagnosis associated with therapy are successfull in doing to disappear symptomatology in one month.

### OXIDATIVE STRESS, REDOX HOMEOSTASIS AND CELLULAR STRESS

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Menière's disease (MD) is characterized by the triad of fluctuating hearing loss, episodic vertigo and tinnitus, and by endolymphatic hydrops found on postmortem examinations. Increasing evidence suggests that oxidative stress is involved in the development of endolymphatic hydrops and that cellular damage and apoptotic cell death might contribute to the sensorineural hearing loss found in later stages of MD. While excess reactive oxygen species (ROS) are toxic, regulated ROS, however, play an important role in cellular signaling. The ability of a cell to counteract stressful conditions, known as cellular stress response, requires the activation of pro-survival pathways and the production of molecules with anti-oxidant, anti-apoptotic or pro-apoptotic activities. Among the cellular pathways conferring protection against oxidative stress, a key role is played by vitagenes, which include heat shock proteins (Hsps) as well as the thioredoxin/thioredoxin reductase system. In this study we tested the hypothesis that in MD patients measurable increases in markers of cellular stress response and oxidative stress in peripheral blood are present. This study also explores the hypothesis that changes in the redox status of glutathione, the major endogenous antioxidant, associated with abnormal expression and activity of carbonic anhydrase can contribute to increase oxidative stress and to disruption of systemic redox homeostasis which can be associated to possible alterations on vulnerable neurons such as spiral ganglion neurons and consequent cellular degeneration.

We therefore evaluated systemic oxidative stress and cellular stress response in patients suffering from Meniere's Disease (MD) and in age-matched healthy subjects. Systemic oxidative stress was estimated by measuring protein oxidation, such as protein carbonyls (PC) and 4-hydroxynonenal (HNE) in lymphocytes of MD patients, as well as ultraweak luminescence (UCL) as end-stable products of lipid oxidation in MD plasma and lymphocytes, as compared to age-matched controls, whereas heat shock proteins Hsp70 and thioredoxin (Trx) expression were measured in lymphocytes to evaluate the systemic cellular stress response. Increased levels of PC (P\0.01) and HNE (P\0.05) have been found in lymphocytes from MD patients with respect to control group. This was paralleled by a significant induction of Hsp70, and a decreased expression of Trx (P\0.01), whereas a significant decrease in both plasma and lymphocyte ratio reduced glutathione GSH) vs. oxidized glutathione (GSSG) (P\0.05) were also observed. In conclusion, patients affected by MD are under condition of systemic oxidative stress and the induction of vitagenes Hsp70 is a maintained response in counteracting the intracellular pro-oxidant status generated by decreased content of GSH as well as expression of Trx. The search for novel and more potent inducers of vitagenes will facilitate the development of pharmacological strategies to increase the intrinsic capacity of vulnerable ganglion cells to maximize anti-degenerative mechanisms, such as stress response and thus cytoprotection







# **KEYNOTE LECTURE 5**

#### FIFTEEN YEARS OF INTRATYMPANIC PRESSURE TREATMENT FOR DISABILITATING MENIERE'S DISEASE

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The local pressure treatment with the Meniett device has been adopted since 1999 in selected cases of definite Meniere's Disease for whom, due to the failure of medical treatment, vestibular neurectomy - as gold standard surgical procedure - had been planned. Although no clear explanation still exists on the mechanism of action, it has been proposed that a local pressure treatment could influence the endolymphatic hydrops by favoring the flow of endolymph towards the endolymphatic sac, thus soliciting it for an enhanced reabsorptive function.

The Rome protocol consisted in 1-month long, self-administered treatment, starting from the day when a ventilation tube was inserted. As mentioned before, only those menieric patients with recalcitrant disease as displayed by an intense recurrence of crises such as 2/3 per weeks or 5 per month during the last three months -, therefore identified as Class D (AAO-HNS, 1995), were selected for a Meniett treatment.

More than 90 subjects were therefore treated between 1999 and September 2015. Each patient was tested with pure tone audiometry, as well as with other eventual Meniere-related tests (depletion test, electrocochleography), before and after the treatment, and they were also asked to fill a diary during the month-therapy, signaling any disturbance related to Ménière's symptomatology. In a limited number of subjects, further 1-month long treatments were needed, due to a relapse of symptomatology after a first period of relief after Meniett treatment. In a last series of subjects, ECochG was used to follow-up the effect of Meniett treatment soon after the end of treatment, as well as at 1, 3 and 6 months after.

The outcome from Meniett treatment was evaluated in the subjects with a least 2-years follow-up (AAO-HNS, 1995) by comparing the pre- versus the post-op disease class (AAO-HNS, 1995). Nearly 65% of the treated subjects had relief from the disease and never needed additional treatment. The electrophysiological data have allowed to hypothesize that such a pressure treatment could actually positively influence the hydropic condition, with a prolonged action.

Meniett treatment has proved to be effective, only mildly invasive (insertion of ventilation tube needed), and worth to be proposed in case of failure from medical treatment, and before a more invasive surgical procedure is taken into consideration.

# **IMMUNE SYSTEM AND MENIERE'S DISEASE**

## LOCAL TREATMENT OF IMMUNE-MEDIATED HEARING LOSS BY ANTI-TNF ALPHA DRUGS

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Objective: To evaluate the local administration of anti-TNFalpha antibodies to the inner ear of patients suffering from autoimmune sensory hearing loss.

Background: Local administration of TNF alpha blocker in an animal model of autoimmune disease prevents inflammation in the cochlea and its associated hearing loss.

Methods: 9 patients presenting with autoimmune sensory hearing loss who responded to oral steroid treatment were implanted with a Silverstein microwick° local delivery system to the round window membrane for 3 to 4 weeks.

Results: 7 patients out of 9 exhibited a stabilisation of their puretone audiometry (PTA) for a period of time ranging from 3 to 15 month. 5 of 9 patients showed an improvement of their hearing threshold. Among the 7 responding patients, 2 of them needed a second treatment which induced a second recovery of the PTA. No toxic effect due to the local administration of the anti-TNFalpha (Remicaid°) treatment were observed.

Conclusion: Local administration of TNFalpha blockers to the inner ear of patients presenting an autoimmune hearing loss allows stabilization or improvement of their hearing function.

# A LOCUS IN CHROMOSOME 6P21.33 ASSOCIATED WITH BILATERAL SENSORINEURAL HEARING LOSS MAY DEFINE IMMUNOMEDIATED VARIANT IN MENIERE'S DISEASE

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Patients with Meniere's Disease (MD) have an elevated prevalence of several autoimmune diseases suggesting a shared autoimmune background (1). The genotyping of large cohorts of patients with several autoimmune diseases has shown that most of these diseases share susceptibility loci (2). However, no consistent loci or genetic marker have been associated with MD and most of the genetic studies were not replicated in an independent cohort of patients. We have used a high density genotyping array, containing 195805 single nucleotide polymorphism and 718 small indels, targeting 186 loci previously associated with 12 autoimmune disorders (Immunochip, Illumina) to explore the association with MD. After QC, 99765 markers and 1587 samples (689 cases/898 controls) remained for further studies. Although no marker reached a genome-wide significant association (p < 10-8), two genomic regions in chromosomes 2 and 6 showed a high number of non-coding SNVs with p0.05, Regulome database information and linkage disequilibrium data. Meta-analysis of both cohorts has identified a small locus with 30 Kb in chromosome 6p21.33 with several associated SNPs (rs9380217 with p-value 1x 10-6 and rs4947296 with p-value 4x 10-6). The locus includes regulatory elements binding sites and the closer genes are DPCR1, MUC21, MUC22, HCG27, CDSN and PSORS1C1. Ongoing work is trying to identify the functional SNPs in the locus. Acknowledgements

This study was funded by PI13/1242 Grant. Sonia Cabrera is supported by Meniere's Society UK, WES-MD Grant. References

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# NEUTROPHIL-TO-LYMPHOCYTE RATIO AND PLATELET TO LYMPHOCYTE RATIO IN PATIENTS WITH ACUTE MENIERE'S DISEASE

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We aimed to investigate the relationship between acute vertigo and inflammation in patients affected by Meniere's Disease (MD) by using the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as an inflammatory marker. We recruited 40 patients with MD (mean age, 49  $\pm$  15 years) who presented to the Otolaryngology Department of University of Bari. We also enrolled 38 age- and sex-matched healthy subjects (mean age, 45 + 10 years) who underwent routine checkups in our hospital. The MD patients were classified as definite MD according ot the AAO-HNS guidelines. NLR and PLR were calculated in all subjects and was compared between the patient and control groups. MD patients presented higher total cholestearol, ESR, NLR and PLR compared to the control group. In conclusion, this study, which is the first to investigate the relationship between the NLR-PLR and MD, demonstrates that the NLR and PLR are significantly higher among MD patients than among healthy controls. This result suggests that the NLR and PLR are novel potential marker of inflammation in peripheral vertigo patients.



## AUTOIMMUNITY AS A CANDIDATE FOR THE ETIOPATHOGENESIS OF MENIERE'S DISEASE: DETECTION OF AUTOIMMUNE REACTIONS AND DIAGNOSTIC BIOMARKER CANDIDATE

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Meniere's Disease is an inner ear disorder that can manifest as fluctuating vertigo, sensorineural hearing loss, tinnitus, and aural fullness. However, the pathologic mechanism of Meniere's Disease is still unclear. In this study, we evaluated autoimmunity as a potential cause of Meniere's Disease. In addition we tried to find useful biomarker candidates for diagnosis. We investigated the protein composition of human inner ear fluid using liquid column mass spectrometry, the autoimmune reaction between circulating autoantibodies in patient serum and multiple antigens using the Protoarray system, the immune reaction between patient serum and mouse inner ear tissues using western blot analysis. Nine proteins, including immunoglobulin and its variants and interferon regulatory factor 7, were found only in the inner ear fluid of patients with Meniere's Disease. Enhanced immune reactions with 18 candidate antigens were detected in patients with Meniere's Disease in Protoarray analysis; levels of 8 of these antigens were more than 10-fold higher in patients than in controls. Antigen-antibody reactions between mouse inner ear proteins with molecular weights of 23-48 kDa and 63-75 kDa and patient sera were detected in 8 patients. These findings suggest that autoimmunity could be one of the pathologic mechanisms behind Meniere's Disease. Multiple autoantibodies and antigens may be involved in the autoimmune reaction. Specific antigens that caused immune reactions with patient's serum in Protoarray analysis can be candidates for the diagnostic biomarkers of Meniere's Disease.

#### EXPERIENCE OF IMMUNOLOGICAL ASPECTS OF MENIERE'S DISEASE

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The correlation between autoimmune disorders and pathology of labyrinthine structures, has been particularly studied in Menière's disease (MD). In spite of the well-known histopathological lesion of MD, an endolymphatic hydrop involving the membranous labyrinthine, its aetiopathogenesis remains an unresolved issue. Vascular alterations, genetic predisposition, hormonal disorders, nutritional and psychological factors might contribute to the genesis of hydrop. For at least two decades, our attention has been focused on the role of the immune system in mediating idiopathic endolymphatic hydrop. In the early'90s, we showed an abnormal immunological pattern in same cases of MD probably due to an aspecific response of immune system, as consequence of an alteration of the normal inner ear homeostasis. Subsequently our studies focused on serum levels of antibodies to laminin, collagen II (CII), collagen I (CI), collagen IV (CIV), and collagen V (CV). The results of this study do not indicate a clear role for this auto-antibodies; they could, however, contribute to the perpetuation of the disease or play a role as a cofactor in association with other mechanisms. In another research we examined the reactivity to bovine inner ear antigens of sera from a series of MD patients. Reactivity to inner ear antigens of molecular weight 44 and 53 kD was found in approximately 40% of the patients. Antibodies to 44 and 53 kD proteins could play a role in the pathogenesis of MD, contribute to perpetuation of the disease and/or play a role as cofactor in association with other mechanisms. Afterwards, in two articles, we evaluated the possible association between MD and the presence of several autoantibodies. We evaluated the association between thyroid autoimmunity and MD, and the possible concomitant presence of thyroid autoantibodies (organ specific autoimmunity) and non-organ specific autoantibodies in a large series of non-selected MD patients. The presence of positive serum autoantibody titres was significantly higher in MD patients as compared to control groups. A statistically significant difference was also observed between MD patients and control groups either regarding organ specific autoimmunity and non-organ specific autoimmunity. Among subjects with positive autoantibody titres, the frequency of organ and non-organ autoimmunity ("mixed" autoimmunity) was almost double, in MD patients as compared to controls. These study demonstrated a significantly increased prevalence of both organ and non-organ specific autoimmunite markers in MD. Recently we studied the vestibular disorders in euthyroid patients with Hashimoto's thyroiditis (HT); our study proved that 52°2% of HT patients showed an alteration of VEMPs and 44•7% of caloric test. A correlation was found between vestibular alterations of HT patients and the degree of serum TPOAb level. This finding suggests that circulating antithyroid autoantibodies may represent a risk factor for developing vestibular dysfunction like hydrop. Probably, in some cases of MD, the precipitation of organ or non-organ specific autoantibody immune-complexes in the inner ear or the autoimmune microangioitis of the labyrinth, could explain the dysregulation of inner ear fluid homeostasis and therefore the pathogenesis of endolymphatic hydrops. In this presentation, we present a review of our twentyfive years research about the role of immune system in Menière's disease.

# **BARANY SYMPOSIUM:** FROM MOUSE MODELS TO CLASSIFICATION OF MB MENIERE

#### THE REGENERATING INNER EAR

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The human inner ear has generally been regarded as an organ with limited regenerative capacity. Unlike mammals, many vertebrates (reptiles, birds, amphibians, and fish) hair cells can be replaced, apparently from surrounding non-sensory supporting cells (Corwin and Cotanche, 1988; Cotanche, 1987; Ryals and Rubel, 1988; Stone and Cotanche, 2007; Taylor and Forge, 2005). Furthermore, studies show that even mammalian vestibular hair cells, including human may regenerate (Forge et al. 1993, Warchol et al. 1993, 1998; Kawamoto et al., 2009); a phenomenon also eminent in clinical practice. Recently, using tissue obtained from trans-labyrinthine neuroma removal, a capacity for hair cell regeneration was found in human vestibular sensory epithelium from "older" individuals (Forge and Taylor et al. 2015) suggesting possible measures to enhance hair cell regeneration in man. Regeneration has not vet been proven in human cochlear sensory epithelium where hair cells appear to have little regenerative capacity. The human cochlea is inaccessible and content delicate. In Uppsala, human cochleae were collected during removal of large, life-threatening petroclival meningioma. It made it possible to analyze fresh human tissue and cells using SEM, TEM, cell and organotypic cultures and immunohistochemistry and cell physiology. Proliferative potential was analyzed using markers such as Ki67, PCNA, Sox2 and p27kip1. At the molecular level organ of Corti cells expressed high levels of cyclin-dependant kinase inhibitors p27 (Kip1) (Löwenheim et al. 1999). We found "supernumerary hair cells" and Ki67/Sox2 positive supporting cells (1.8% – unpublished data). It was unforeseen to discover neurospheres and differentiating neurons from freshly obtained adult cochleae harvested at surgery. Findings may suggest a low-grade cell turn over in the human cochlear sensory epithelium and can support strategies to induce regeneration to treat deafness in man.

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## EXPERIMENTAL INDUCED HYDROPS - IN VIVO STUDIES IN MICE

M. Magnusson Lund, Sweden

#### CLASSIFICATION OF MB MENIERE, A PROGRESS REPORT

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#### IT THERAPY FOR MD

M. Magnusson Lund, Sweder



7<sup>th</sup> International Meniere's Disease Inner Ear Disorder



# **KEYNOTE LECTURE 6**

## CEREBRAL VENOUS INSUFFICIENCY IN MENIERE'S DISEASE

**R** Filino Rome, Italy

To analyze the presence of chronic cerebrospinal venous insufficiency parameter and vascular abnormalities, in the internal jugular veins (IJVs) and/or vertebral veins in sitting and supine posture, in patients with Meniere's Disease compared to healthy general population. A prospective study on 32 patients affected by definite Ménière was performed from February 2012 to January 2013. All subjects underwent an echo-color Doppler examination of the cerebrospinal venous flow. 21 of the 32 Menieric patients showed a statistically significant reflux in the intracranial veins versus healthy (65.6 vs 25%; P < 0.001). A high prevalence of IJVs stenosis with hemodynamic changes (increased velocity or absence of flow) was observed (66.7 vs 33.3%; P < 0.05). The other parameters considered did not show statistically significant differences among the two groups. The results obtained showed a vascular pattern of cerebrospinal venous system present in patients affected by definite Meniere. This vascular impairment significantly affects the vascular areas more directly involved in the venous drainage of the inner ear. Thus venous stasis may be considered a further pathogenetic mechanism for development of Meniere's Disease.

# **VENOUS CONGESTION IN MENIERE'S DISEASE**

### CHRONIC CEREBRO-SPINAL VENOUS INSUFFICIENCY IN MENIERE'S DISEASE: DIAGNOSIS AND ENDOVASCULAR TREATMENT AFTER 24-MONTH FOLLOW-UP

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Introduction: To evaluate by the means of Doppler ultrasound, MRI and phlebography the relationship between Meniere's Disease and chronic cerebrospinal venous insufficiency (CCSVI) and to test whether angioplasty is an effective procedure in improving symptoms. Materials and Methods: 1) Phase 1: 172 patients diagnosed with definite Meniere's Disease (AAO 1995) who had gained no benefit by medical therapy, underwent echo-enhanced color Doppler sonography using the Zamboni protocol to check for CCSVI. 100 healthy subjects matched for age and gender acted as controls. 2) Phase 2. In 60 of ECD positive Meniere' cases we performed a venogram and the diagnosis of associated CCSVI was confirmed. These patients were treated by angioplasty of the Internal Jugular Vein, then re-tested respect the baseline scales of Meniere's Diseases. Twenty of them had a 24-month follow.up. Results: Out of a total of 172 patients with Meniere's Disease, an ultrasound diagnosis of CCSVI was made in 150/172 patients (87.2%). In the healthy population, was found in only 10% of cases. In 60 patients venography confirmed the CCSVI diagnosis and PTA proved to be effective in 80% of patients, with significant improvement of audiological and vestibular function at 24 month follow-up. Conclusions: The prevalence of CCSVI in patients with Meniere's Disease is higher than in healthy subjects; PTA seems useful because of an improvement in symptoms with audiological and vestibular functions better in the majority of patients.

# IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS AND MENIERE SYNDROME: THE ROLE OF CEREBRAL VENOUS DRAINAGE

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Background: the etiology and the pathogenesis of idiopathic sudden sensorineural hearing loss (ISSHL) and Ménière syndrome (MD) still remain unclear. Many hypotheses (viral, immunologic, vascular, etc) have tried to disclaim the problem of their origins. Aim: to evaluate the influence of cerebral venous drainage on the pathogenesis of these two clinical entities. We enrolled 59 consecutive patients (32 males, mean age 53.05 + 15.37 years): 40 suffering from ISSHL (22 males, mean age 53.27 + 17.28 years) and 19 from MD (10 males, mean age 52.28 + 10.68 years). 30 healthy controls (15 males, mean age 52.63 + 14.83 years) were also enrolled. All underwent physical and clinical examination, biochemical evaluation (glycemic and lipid profile, viral serology, C reactive protein, etc), audiometric (tonal, vocal, vestibular evoked myogenic potentials [VEMPs] auditory brainstem response [ABR] test) and impedance audiometry examination. The pure tone average (PTA) was calculated for the following frequencies: 250, 500, 1000, 2000, 3000, 4000, 8000. An echo color Doppler evaluation of the venous cerebral veins, internal jugular (IJV) and vertebral veins (VV) at supine and 90° position was performed. The mean, maximum and minimum veins velocities of the extracranial veins were calculated and compared among groups. Cerebral and extracranial veins morphology and functions were assessed. No morphological alterations were found both in patients and controls. There were no signs of stenosis, blocked flow, membranes, etc. We found lower minimum, mean and maximum velocities in distal IJVs (p=0.013; p=0.012; respectively) and left VVs (p=0.027; p=0.008; p=0.001; respectively) in supine  $(0^{\circ})$  position in both MD and ISSHL patients as compared to controls. The same was for orthostatic position (90°). Furthermore, we found negative correlations between the velocities in extracranial veins and PTA values: therefore, the worst the audiometric performance of the subjects, the lower the velocities in the venous cerebral drainage. ISSHL and MD patients showed altered venous flow in IJVs and VVs as compared to controls, independently from posture. This different behavior of venous tone control can influence the ear performance and may have a role in the pathogenesis of both diseases.

# ENDOVASCULAR TREATMENT OF VERTIGO CAUSED BY JUGULAR BULB ABNORMALITIES

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Jugular bulb abnormalities can induce tinnitus, hearing loss, or vertigo. Vertigo can be very disabling and may need surgical treatments with risk of hearing loss, major bleeding or facial palsy. Hence, we have developed a new treatment for vertigo caused by jugular bulb anomalies, using an endovascular technique.

Four patients presented with severe vertigo mostly induced by high venous pressure. One patient showed downbeat vertical nystagmus during the Valsalva maneuver; another exhibited VEMP at low threshold. The temporal-bone CT scan showed a high rising jugular bulb or a jugular bulb diverticulum with dehiscence and compression of the vestibular aqueduct in all cases. In each case, we plugged the upper part of the bulb with coils, and we used a stent to maintain the coils and preserving the venous permeability.

After 1 to 5 years of follow-up, those patients experienced no more vertigo, allowing return to work. The 3-month arteriogram showed good permeability of the sigmoid sinus and jugular bulb through the stent, with complete obstruction of the upper part of the bulb in all cases.

Disabling vertigo induced by jugular bulb abnormalities can be effectively treated by an endovascular technique. This technique is minimally invasive with a probable greater benefit/risk ratio as compared to surgery.





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# **VESTIBULAR MIGRAINE**

#### VERTIGINOUS MIGRAINE AND MENIERE'S DISEASE

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Beginning in 1992 our group has published on genetics of Menière's disease. We have observed in the first family we published the association of headache with the symptoms of Menière's disease. This associated headache was carefully studied and classified as migraine according to the International Headache classification in our second family published in 1997. From then on all the families we published with several siblings affected by Menière's symptoms also had migraine. In 2002 we published 6 families with several siblings affected by Menière's symptoms and migraine. Some had full blown classic Menière's syndrome and migraine. Some had only Menière's symptoms, some had mainly migraine. The index patients in all these families had full blown Menière's yndrome and migraine. We followed the 1997 family for twelve years and we found that patients with only migraine in 1997 later had the Menière's symptoms and therefore there was an evolution from migraine alone to classic Menière's syndrome in some siblings. Based on these findings we postulate that migraine, vertiginous migraine and Menière's disease may be part of a continuum caused by genetic predisposition allied with lifestyle and environmental factors. We are currently studying the molecular genetics of the 1997 family in cooperation with the Seidman laboratory of molecular genetics of Harvard Medical School. Problably a single gene mutation is present in affected patients.

## VESTIBULAR MIGRAINE IN AN OTOLARYNGOLOGY CLINIC: PREVALENCE, ASSOCIATED SYMPTOMS, AND PROPHYLACTIC MEDICATION EFFECTIVENESS

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To assess the prevalence of vestibular migraine (VM) in patients consulting to an otolaryngology clinic, the neurootological associated symptoms, and the effect of prophylactic antimigrainous medication on VM symptom improvement.

Study Design: Retrospective chart review.

Setting: Tertiary referral otolaryngology clinic.

We used the diagnostic criteria from the Bárány Society and the International Headache Society to allocate patients to a subgroup: VM, possible VM, and atypical VM.

The prevalence of VM, percentages of associated neurotological symptoms, and percentages of effectiveness of prophylactic medication.

Sixty-five (16%) patients were selected from the total patient population (n = 407) from which 4.2% were assigned to the definite VM group, 5.7% to the probable VM group, and 6.1% to the atypical VM group. We found a significantly different distribution between the groups for photophobia (p = 0.035), ear pressure (p = 0.023), and scotoma (p = 0.015). Thirty patients were administered with flunarizine and 68% responded with an improvement in VM symptoms (p G 0.001). For propranolol, 31 patients were treated and there was an improvement of symptoms in 73% (p < 0.001). Remarkable was the fact that these percentages were not significantly different between the subgroups.

VM is a common disorder presenting in a dizziness clinic, and detailed history taking is important to assess VM-associated symptoms and thus to prevent underdiagnosis. The latter is very important because our study shows that the majority of patients, regardless of VM subtype, can benefit from a prophylactic treatment, but further prospective studies are necessary.

# VESTIBULAR ASSESSMENT IN MENIERE'S DISEASE AND MIGRAINE

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Meniere's Disease is still one of the most important vertiginous disorders. Introduction of new vestibular assessment methods has influenced our understanding of peripheral vertiginous diseases and their differential diagnoses. Migraine and Meniere's Disease are the two important disorders which needs differential diagnosis. VNG (videonystagmography), caloric testing, cVEMP (cervical vestibular evoked myogenic potentials), oVEMP (ocular vestibular myogenic potentials), vHIT (video head impulse test) and posturography has been used in the assessment of vestibular disorders, one of which is Meniere's Disease. In this cohort, the vestibular assessment outcome of the patients with Meniere's Disease who were seen in an outpatient setting were presented.

# JAPANESE SOCIETY OF EQUILIBRIUM RESEARCH (JSER) SYMPOSIUM

# **INTRODUCTION**

Mamoru Suzuki Tokyo Medical University, Tokyo, Japan

Meniere's Disease is a well-known vestibular disorder comprising approximately 10% of dizzy patients in Japan. The nationwide study group had been organized in 1974 under the support of the Health and Labor Science Research Grant for Research on Specific Disease (Vestibular Disorders) from the inistry of Health, Labor and Welfare, Japan. Through this study, epidemiological trend, animal model, diagnostic criteria, and treatment measures were established. It is our great pleasure to present some of our results that the study group had been engaged in for such a long period. We have 4 topics, epidemiology, diagnostic guideline, diagnosis using RI and treatment modality which are presented by the experts in each field. This session will hopefully deepen our understanding of Meniere's Disease of which etiology is not fully known.

# EPIDEMIOLOGICAL CHARACTERISTICS OF MENIERE'S DISEASE IN JAPAN

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From 1975 to 2014, nationwide, multi-center surveys on Meniere's Disease were performed by the Research Committee of Meniere's Disease and the Research Committee of the Peripheral Vestibular Disorders. De novo definite Meniere's Disease cases were sampled by the members of the Committees. The transition of the epidemiologic characteristics of the Meniere's Disease were analyzed and compared over times. In the Meniere's Disease, the male to female ratio has changed from even to female predominance. With respect to onset age at disease, the incidence in elderly patients (age  $\geq$  60 years) was increased when we corrected for age distribution in the overall population.





#### DIAGNOSIS 1: DIAGNOSTIC STANDARD FOR MENIERE'S DISEASE BASED ON THE CLINICAL GUIDELINE OF THE DISEASE IN JAPAN

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The clinical guideline for Meniere's Disease in Japan was published in 2011 by The Vestibular Disorder Research Committee of Japan with the support of the

Ministry of Health Labor and Welfare of Japan. In the guideline, the diagnostic criteria of Meniere's Disease are classified into three categories, definite Meniere's Disease, atypical Meniere's Disease of the cochlear type and atypical Meniere's Disease of the vestibular type. In the criteria, the concept of Meniere's Disease is described as a vestibular and cochlear disorder with the primary etiology of endolymphatic hydrops.

- 1. Definite Meniere's Disease:
- Repeated attacks of vertigo accompanied with aural symptoms, such as hearing loss, tinnitus and/or ear fullness.
- 2. Atypical Meniere's Disease of the cochlear type:
- Repeated aural symptoms, such as hearing loss, tinnitus and/or ear fullness, without vertigo.
- 3. Atypical Meniere's Disease of the vestibular type:

Repeated attacks of vertigo similar to definite Meniere's Disease, without the fluctuating aural symptoms associated with the vertigo

Because there are many cases of vertigo due to an unknown cause, diagnosis of this type should be limited only to cases with a high possibility of endolymphatic hydrops based upon the clinical history and neurotological examination. Diagnosis

- 1. Because it is very difficult to differentiate the first attack of Meniere's Disease from sudden deafness with vertigo, confirmation of the second attack or repeated attacks by follow-up is necessary for the diagnosis of Meniere's Disease.
- 2. Diseases indicating symptoms similar to Meniere's Disease for which the cause is clear, such as perilymph fistula, inner ear syphilis, vestibular schwannoma, neurovascular compression syndrome, cerebellar and brain stem diseases, etc., should be excluded from the diagnosis of Meniere's Disease in each of the categories.
- 3. For the purpose, neurological and neurotological examinations, including balance test, auditory brainstem response, and image diagnosis, such as CT and MRI, are necessary when required.
- 4. For the evaluation of endolymphatic hydrops, it is recommended to perform glycerol test, furosemide test or electrocochleogram (ECochG).

Vertigo

- 1. Although the duration of vertiginous episode varies between individuals, it generally lasts from about 10 minutes to several hours. Cases with transient episodes, i.e., < one minute, should be excluded from the diagnosis of Meniere's Disease.
- 2. In many cases, horizontal-rotary nystagmus is observed during the attacks.
- 3. Cases accompanied by central nervous disorders, such as unconsciousness, double vision, speech disorder, etc., are excluded from the diagnosis of Meniere's Disease.
- 4. The frequency of vertigo attacks varies between individuals, from several times per week, in the most frequent cases, to several times per month or year.

Aural symptoms

- 1. In many cases of Meniere's Disease, aural symptoms occur just before or simultaneous with the vertigo attack, and worsen according to the attack and improve after the end of the attack.
- 2. Although the main aural symptoms are hearing loss and tinnitus, some patients complain of sensitivity to sound.
- 3. The sensorineural hearing loss fluctuates with the disease stage.
- 4. Although the hearing loss is unilateral in the primary stage, bilateral hearing loss occurs in twenty to thirty percent of the cases depending upon protraction of the disease (bilateral Meniere's Disease).

I would like to describe the diagnostic criteria of Meniere's Disease in Japan, from the basic concept(s).

## DIAGNOSIS 2: DIAGNOSIS OF ENDOLYMPHATIC HYDROPS USING 3T MRI IN PATIENTS WITH MENIERE'S DISEASE

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Meniere's Disease (MD) has been thought to be attributable to endolymphatic hydrops (ELH), but this has only been confirmed histopathologically after death. Therefore, along with clinical symptoms, clinical tests suggestive for ELH are usually used for diagnosis. However, even if functional testing is performed, the results are still indirect proof. Meanwhile, recent advances in imaging by three-dimensional, fluid-attenuated inversion recovery (3D-FLAIR) of magnetic resonance imaging (MRI), in association with enhancement by gadolinium-based contrast agents (GBCAs), enables visualization of ELH in patients with MD. We have succeeded in visualizing ELH semi-quantitatively in patients with MD, by using bilateral intratympanic GBCA administration with MRI. To visualize endolymphatic hydrops in patients with MD, including the patients who met the American Academy of Otolaryngology-Head and Neck Surgery criteria for "definite" MD, "possible" MD, atypical MD patients (who had fluctuating low frequency sensorineural hearing loss without vertigo), and acute low-tone sensorineural hearing loss patients, were evaluated. 3D-FLAIR MRI clearly showed that the GBCA successfully penetrated the round window membrane, entering the perilymphatic space and delineating the GBCA-enhanced perilymphatic and GBCA-negative endolymphatic spaces of the inner ear. Almost all "definite" MD patients showed ELH. Furthermore, ELH was also demonstrated in some of "possible" MD, "atypical" MD, and acute low-tone sensorineural hearing loss patients. Such image-based diagnosis will lead to re-revaluation and reclassification of the diagnostic criteria for MD.

#### OVERVIEW OF THE TREATMENT OF MENIERE'S DISEASE IN JAPAN

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Meniere's Disease (MD) is a disorder of the inner ear affecting hearing and balance to a varying degree. It is characterized by episodes of vertigo attacks lasting more than 20 minutes (10 minutes in Japan), low-pitched tinnitus, hearing loss, and a feeling of fullness in the ear. There is currently no gold standard treatment for MD. Endolymphatic hydrops may represent the histological inner ear findings in most patients.

A variety of medical and surgical treatments have been developed to treat or control the symptoms. No cure exists for MD. Treatment can be divided into non-destructive and destructive procedures. Non-destructive procedures aim to reduce the symptoms of MD through dietary restrictions as well as through the use of diuretics. Isosorbide is usually used as a diuretic mainly to treat hydrocephalus and glaucoma. In Japan, isosorbide is also used for MD to improve endolymphatic hydrops. As for destructive procedures, surgical decompression of the endolymphatic sac, surgical or chemical labyrinthectomy, and vestibular nerve section are applied for intractable cases. During the 1970s, Inglestadt et al. observed that some patients reported improvement with pressure changes in a pressure chamber (Acta Otolaryngol 1976; 82: 368-378). Densert et al. showed that manipulation of middle ear pressure influences inner ear pressure (Acta Otolaryngol 1975; 80: 93-100). Later, improvement in vertigo and hearing in patients with MD was described after application of positive pressure to the middle ear. These reports eventually led to the development of the Meniett® device. However, in Japan, medical practitioners have been required to import Meniett® devices themselves to provide this middle ear pressure treatment because they have not been cleared by the Ministry of Health, Labour and Welfare of Japan. A tympanic membrane massage (TMM) device is an intermittent pressure treatment device initially used in western European countries in the late 19th century for patients with otitis media with effusion (OME) and without tympanotomy. In Japan, the TMM device has been cleared for use in patients with OME by the Ministry of Health, Labour and Welfare of Japan, and currently, medical practitioners can buy this pressure pulse generator device (Tympanic Massage Unit) from a domestic supplier. In this symposium, the current status of treatment procedures for patients with MD in Japan will be presented.





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# **VESTIBULAR REHABILITATION**

# PRINCIPLES OF LONG-TERM VESTIBULAR REHABILITATION

Mlacour Marseille, France

The lecture questions the relationships between the plastic events responsible for the recovery of vestibular function after a unilateral vestibular loss, that is, the vestibular compensation process which has been well described in animal models in the last decades, and the vestibular rehabilitation therapy elaborated on a more empirical basis for vestibular loss patients.

The main objective is to provide clinicians with an understandable view on When and How to perform vestibular rehabilitation, and to explain Why vestibular rehabilitation may benefit from basic knowledge and may influence the recovery process.

With this perspective, 10 major recommendations are proposed as ways to identify an optimal functional recovery rather than to give a catalog of results. Among them are the crucial role of active and early vestibular rehabilitation therapy, coincidental with a post-lesion sensitive period for neuronal network reorganization, and the instructive role that vestibular rehabilitation therapy may play in this functional reorganization when it is performed during this opportunity time window. The need for progression in the vestibular rehabilitation therapy protocols, and the necessity to base these protocols mainly on adaptation processes rather than on habituation exercises are underlined. Why it is important to take into account the sensorimotor and cognitive profile of the patient. and why customized or "à la carte" vestibular rehabilitation should be preferred to standardized protocols are also emphasized. Last but not the least, vestibular rehabilitation therapy protocols should be aimed at reducing anxiety and stress, and motivating the vestibular loss patients. Ecologic contexts can be used as a way to achieve these latter goals.

More than ten general principles are likely, but these principles seem crucial for the fast recovery of vestibular loss patients to ensure good quality of life.

## ROLE OF PERINEURONAL NETS IN VESTIBULAR COMPENSATION

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Perineuronal nets are aggregates of extracellular matrix molecules surrounding several types of neurons in the adult CNS, which contribute to stabilising neuronal connections. Interestingly, in conditions associated with plasticity in the adult brain, a reduction of PNNs has been observed. However, it is not known whether PNN changes are functional to plasticity and repair after injury. To address this issue we investigated PNN expression and anatomical remodelling in the vestibular nuclei of the adult mouse during vestibular compensation. Vestibular compensation refers to the resolution of postural and oculomotor deficits resulting from a peripheral vestibular lesion. We found that following unilateral labyrinthectomy, static postural functions of the mouse recuperate in 2 weeks, while dynamic reflexes in 4 weeks. Remarkable structural plasticity of glutamatergic and GABAergic fibres was observed in the lateral vestibular nucleus on both sides at different time points after unilateral labyrinthectomy, which may contribute to functional recovery. Moreover, PNNs appeared strongly attenuated during the course of vestibular symptoms amelioration, while they were completely restored once vestibular deficits had fully recovered. Interestingly, in mice with genetically defective PNNs vestibular compensation was accelerated. Overall, these results indicate that plasticity mechanisms underlying vestibular compensation depend crucially on PNN modulation.

# DEVELOPMENT OF VESTIBULAR REHABILITATION PLATFORM USING IMMERSIVE VIRTUAL REALITY SYSTEM

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Virtual reality (VR) system has been rapidly incorporated into several novel platform in the fields of medical education, surgical simulation, psychiatric disability or physical rehabilitation. The use of VR to enhance vestibular rehabilitation is also not emerging concept. However, VR-based vestibular rehabilitation mostly has been adapted at multiscreen environment with the large cave, which requires high cost and large space. In contrast, head mount display (HMD) based VR system could provide more immersion as compared to multiscreen based VR and allow the user the ability to move more freely. We developed the vestibular rehabilitation platform using immersive HMD-VR system connected with eye and head inertial-tracker, which may bring about innovation for vestibular rehabilitation with its interactive system and sense of reality. Eye tracking HMD (upgrade package model for oculus rift DK2, SMI, Teltow, Germany) were used for innovative vestibular rehabilitation platform. Each condition for vestibular rehabilitation-1) Active eye-head movement with visual target, 2) habituation exercise to pathologic response, 3) balance gait exercise and 4) general conditioning exercise- was created as virtual reality, which was made by the Unity 3D program (Unity technologies, CA, USA). Stream of eye and gaze movement of user during vestibular rehabilitation was analyzed by Visual C++ program in real time, which was used as interface for sensory feedback based on user action. Our innovated VR- based vestibular rehabilitation platform provides 1) sensory feedback using eye and head inertial tracking system without constraints like space limitation or high cost and 2) exciting condition with immersive virtual system, which may enhance the effectiveness of vestibular rehabilitation as compared to conventional methods .

# REDUCTION OF TIME CONSTANT BY A NOVEL VESTIBULAR HABITUATION: POSSIBILITY AS A POTENT COUNTERMEASURE FOR TREATMENT OF PATIENTS WITH MOTION SICKNESS

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We schemed out a novel habituation method using opposing visual and vestibular stimuli for reduction in Time Constant (TC). The aim of this study is to investigate whether our novel vestibular habituation (VH) method could effectively reduce TC in healthy subjects prior to clinical implication for patients with motion sickness (MS). Experiments were performed with an earth vertical axis rotation system. We designed 2 paradigms for reduction in TC using outof-phase optokinetic (OK) stimuli. 12 healthy subjects (M:5, F:7; mean age: 26 yrs) participated in the study. For VH, 7 patients (M:3, F:4) were rotated with rotational velocity of 20 °/sec. Habituation protocol was unidirectional (clockwise) 2 paradigms including a series of (1) per rotatory aVOR cancellation using OK drum moving at 25°/sec to the same direction as chair, (2) post rotatory aVOR cancellation using stationary OK drum, followed by chair stop. Each series was conducted once per day for 3 consecutive days. 5 patients (M:3,F:2) were exposed to the rotation velocity at 20°/sec as control group in the same manner as that of experimental group (sham habituation). TCs (TCcw and TCccw) of all subjects were obtained from step velocity test before and after habituation session

Before and after VH, TCcw were 16.73 + 0.62 s and 11.74 + 1.2 s, and TCccw were 17.44 + 1.03 s and 11.95 + 1.02 s respectively, which showed statistically significant reduction (p < 0.005). In contrast, there were not statistically significant differences of TCs between before and after sham habituation in control group. Reduction of VOR gain was not observed in both groups. Our novel VH could suggest the possibility as a potent countermeasure for treatment in patients with MS. In particular, TC after VH was shorter for both direction even though unidirectional stimulation was given, which could give helpful basis for designing the VH protocol for clinical implication. On the other hand, VOR gain was not affected by vestibular habituation and must be substantiated by further studies on a large scale.



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# SUDDEN HEARING LOSS & PERILYMPHATIC FISTULA & OTOTOXICITY

## OTOACOUSTIC EMISSIONS IN SUDDEN SENSORINEURAL HEARING LOSS

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Objective: To evaluate the role of otoacoustic emissions (OAEs) in the prediction of idiopathic sudden sensorineural hearing loss (ISSNHL) outcome.

Study Design: Open-label prospective study.

Setting: Tertiary referral medical center.

Patients: Fifteen ISSNHL patients (age: 57.6 T 16.2 years) were prospectively followed 7 days, 14 days, and 3 months post presentation and the commencement of treatment.

Intervention: Pure-tone audiometry, TEOAEs (Transient Evoked OAEs), and DPOAEs (Distortion Product OAEs) testing.

Main Outcome Measures: The pure-tone threshold averages of the three most affected frequencies, detectability, and the signal to-noise ratios (SNRs) values of the TEOAEs and DPOAEs were calculated. The main outcome measures were pure-tone hearing improvement, sensitivity, and specificity of the OAEs measures towards ISSNHL outcome.

Patients having detectable TEOAEs on the first follow-up evaluation had average hearing improvement of 62 + 41% whereas those with no response improved only by 11 + 15% (p < 0.001). For the DPOAEs hearing improvement, results were 71 + 37% and 10 + 14%, respectively (p < 0.001). The sensitivity of recordable TEOAEs on the seventh day of follow-up towards the prediction of significant hearing improvement reached 71% and the specificity 100%. For the DPOAEs, the corresponding values were 83% and 100%. Univariate analysis showed significant contribution for the variance in hearing improvement by both TEOAEs and DPOAEs and their interaction (p values of 0.043, 0.005, and 0.009, respectively).

The results suggest potential role of TEOAEs and DPOAEs evaluation in the early stage of treatment in the prediction of ISSNHL outcome.

## MRI FINDINGS AND COMPLIANCE TO PERFORM MRI IN PATIENTS WITH SSNHL

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Due to the relatively high prevalence of vestibular schwannoma among patients with sudden sensory neural hearing loss (SSNHL) MRI is recommended in these patients. Nevertheless MRI is still not always performed and the correct diagnosis is done years later in some cases.

Aims of study: To evaluate MRI performance in patients who suffered an event of SSNHL and the rate of pathologic findings in these patients.

150 consecutive patients who suffered an event of SSNHL are included in the study. Upon the diagnosis of SSNHL appropriate explanation was given to the patient and a letter was sent to the family physician and ENT specialist in the community. Patients were schedule to the outpatient clinic, and their charts were reviewed several months later to examine whether MRI was performed. Those who did not undergo the examination were re-asked to do it

Of 150 patients 18 (12.6%) were lost for follow up during the study period whereas 132 patients were available for follow up. Compliance for MRI performance in patients with SSNHL was 85.6%. An absolute contraindication (metal implant) justified it in only one of these patients. Prevalence of significant MRI findings in patients with SSNHL was 8.4%. Prevalence of vestibular schwannoma was 3.0%.

The need to perform MRI in patients with an event of SSNHL should be clearly explained to patients, family physicians and insurance authorities in order to meet criteria for standard medical care and to avoid unjustified late diagnosis of vestibular schwannoma.

# EFFECT OF THE HEARING LEVEL OF NON AFFECTED EAR AND SEVERITY OF ACUTE HEARING LOSS IN PATIENT WITH UNILATERAL SUDDEN DEAFNESS FROM THE PERSPECTIVE OF TINNITUS

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Objective: We aimed to evaluate the influence of hearing level of non affected ear and severity of hearing loss for acute-onset tinnitus in patients with unilateral idiopathic sudden sensorineural hearing loss (ISSNHL). Methods: A total 478 patients with ISSNHL were enrolled retrospectively and the medical records reviewed. Patients were classified into two groups according to the presence of acute-onset tinnitus at the initial examination. Pure tone average (PTA) in four frequencies (0.5, 1, 2, 4 KHz) were calculated for the both ear, the level of hearing loss classified into five group (mild, moderate, severe, profound or deaf) and correlated with onset of tinnitus. Also, patients classified into two group according hearing level of non effected ear ( with or without loss) and correlated with onset of tinnitus. Results: A total 68% (n = 314) of patients with sudden deafness had tinnitus initially. There were correlations of onset of tinnitus and severity of hearing loss and hearing level of opposite ear (Spearman correlation coefficient: -0.97, 0.02 respectively, significancy 0.05, 0.01 respectively). Conclusion: Worse contralateral hearing and severity of hearing loss were associated with an increased incidence of concurrent tinnitus.

# LONG TERM TRANSTYMPANIC STEROID TREATMENT RESULTS IN PATIENTS WITH ACUTE COCHLEAR HEARING LOSS

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Systemic steroid therapy is the standard treatment for acute cochlear hearing losses. Intratympanic steroid injections are generally preferred as a maintenance treatment or sometimes as the first option for cases in which the side effects limit systemic steroid administration. In this study, hearing results of patients with acute cochlear hearing loss who showed limited or no response to systemic and intratympanic steroid treatments and received salvage transtympanic steroid treatment (TTST) through a ventilation tube (VT) were evaluated.

The records of 43 patients with acute cochlear (sensorial) hearing loss, who received long-term TTST through VT with the diagnoses of sudden sensorineural hearing loss (SSHL), Meniere's Disease (MD) and acute low tone sensorineural hearing loss (ALTSNHL) were examined retrospectively. All cases received standard systemic steroid treatment at first with a dose of 1 mg/kg after audiological testing and confirmation of no retrocochlear pathology with MRI. They were decided to receive TTST due to the ongoing hearing losses which showed limited or no response to systemic steroid treatment. VT was placed in the posterior inferior guadrant of the tympanic membrane and 5 drops of dexamethasone (0.25 mg/cc) once in a day were administered into the external auditory canal of the patients. The patients were advised to lay on their sides with the treated ear up for 20 minutes while putting the ear drops into their ears. Toynbee maneuver was taught in order to facilitate passage of the drops into to the middle ear through the VI. In this way the applications were continued for 3 months. The average bone conduction thresholds in 500, 1000, 2000 and 4000 Hz frequencies of before and at the end of 3rd month were calculated and compared, an improvement of more than 10 dB was considered as significant. The cases who had a  $\leq$  30 dB speech reception threshold difference and  $\leq$  15% speech discrimination score between the affected and the healthy ears were considered as having serviceable hearing. Hearing improvements were also classified according to Siegel's criteria.

There was significant improvement in the hearing of 9 of 15 (60%) patients with SSHL. Significant improvement also occurred in the hearing of 12 of 22 (54.5%) patients with MD. Significant hearing improvement was observed in 4 of 6 patients (66.7%) with ALTSNHL. As a result, hearing was significantly improved in 25 of 43 patients (% 58.1) who received TTST through VT for 3 months; in 16 of these patients (% 64) the final hearing levels were serviceable. Complete improvement occurred in the hearing of 13 patients (%52) according to Siegel's criteria.

Intratympanic injections, applications through VT or laser myringotomy and continuous minipump delivery may be used for the purpose of avoiding systemic side effects of long term systemic steroid treatment. Long-term and high doses of perilymph steroid concentration may be provided by these methods and treatment can be continued as long as it is required. It is revealed in this study that, significant and serviceable hearing improvement can be provided by long-term TTST administration through VT in acute cochlear hearing losses. However, comparing the results of treatment of a similar group who received no treatments may provide further information.





#### THE SPONTANEOUS PERILYMPH FISTULA CONUNDRUM- DO WE FINALLY HAVE AN EXPLANATION?

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Spontaneous perilymph fistula (PLF) is uncommon. An improvement in symptoms and signs following patching of the round and oval window region, is felt to demonstrate presence of fistulae. Opponents stress that exploration of the middle ear fails to demonstrate leakage of perilymph from the round or oval windows. Histological temporal bone studies have failed to reveal open defects in otic capsule bone. The occurrence of spontaneous PLF therefore is currently in doubt.

There are however patients who have symptoms of incapacitating vertigo, fullness, fluctuating hearing loss, Tullio phenomenon, disequilibrium, intolerance to sounds, and who are exquisitely sensitive to changes in barometric pressure. Several have a history of head injury. The fistula sign is positive in some cases. CT scans (HRCT) in these cases consistently fail to reveal the presence of a superior (SSCD), or posterior semicircular canal dehiscence (PSCD) syndrome.

Between 2009 and 2013, ten patients (n=10) underwent middle ear exploration for the above-mentioned symptoms. All patients underwent detailed objective testing at the vestibular and balance laboratories at the University of Louisville, or the Heuser Hearing Institute. All patients also underwent HRCT, and magnetic resonance imaging (MRI) to rule out other etiologies. Surgery was performed under general anesthesia. The round and oval windows were observed at high magnification along with stapes palpation for perilymph leakage. A Valsalva maneuver was then carried out. After gently denuding the mucosa around the OW and RW, lobule fat was packed in the two niches.

Of the ten patients explored, only one had true perilymph leakage. Perilymph leakage was not demonstrated in the nine patients (n=9). However close observation in these demonstrated a membranous footplate instead of bone. One case failed but was helped at revision surgery. None of the cases demonstrated an appreciable drop in hearing. On reviewing the HRCT and using the "invert" function, one may be able to demonstrate these deficiencies in the footplate preoperatively.

We report for the first time findings of a defect in stapes footplate which is covered by a membrane as a possible etiology for symptoms. This finding may explain causation of symptoms in the absence of true perilymph leakage. Curative surgery involves patching defect and provides subjective and objective relief.

#### CHRONIC DISEQUILIBRIUM AS MAIN SYMPTOM OF BILATERAL PERILYMPH FISTULA - CASE PRESENTATION

#### N. Arsovic, D. Pavlovic

Faculty of Medicine, University of Belgrade, Clinic for Otorhinolaryngology and Maxillofacial Surgery, Clinical Centre of Serbia, Belgrade

Introduction Perilymph fistula is diagnostic challenge because of diverse clinical presentation and no specific tests. Methods and Results We present a patient with history of chronic disequilibrium, difficulties in concentration, depression with no ability to work and obviously ruined quality of life. He had history of few head traumas. Recurrent BPPV could't explain his clinical picture. Positive Step Side Test (SST) was indication for exploratory tympanotomy. After sealing the oval window, patient improved rapidly. Conclusion History of chronic disequilibrium, head trauma and positive SST should rise suspicion to perilymph fistula.

# INTRATYMPANIC DEXAMETHASONE: POTENTIAL IN THE PREVENTION OF CISPLATIN OTOTOXICITY

A. Shupak, T. Marshak, L. Levi, M. Steiner Unit of Otoneurology Lin Medical Center, Department of Otolaryngology - Head & Neck Surgery Carmel Medical Center, Department of Oncology, Lin Medical Center, The Bruce Rappaort Faculty of Medicine, The Technion, Haifa, Israel

Objective: To examine the role of intratympanic Dexamethasone (ITD) in the prevention of Cisplatin-induced hearing loss. Study Design: Prospective randomized controlled clinical trial. Setting: Tertiary referral center.

Twenty-six patients suffering from a neoplastic disease for which the treatment protocol included Cisplatin were recruited. Prior to each Cisplatin treatment session ITD was injected to the baseline randomly assigned ear while the other ear of the same patient served as the control. Audiometry and Distortion Product Otoacoustic Emissions (DPOAEs) test results of the baseline and follow-up examinations were compared within and between the study and control ears. The cumulative dose of Cisplatin was greater than 400 mg for the fifteen subjects that completed the study. The pure tone threshold at 8000 Hz and pure tone average threshold at 4000-8000 Hz significantly increased in both the study (p<0.005, p<0.03 respectively) and control ears (p<0.01, p<0.005 respectively). Significant increase in the pure tone threshold for 6000 Hz was observed in the control (p<0.02) but not in the study group. Within the groups comparison also revealed significant decrease in the DPOAE average signal-to-noise ratio (SNR) for the f2 frequencies 7031 (p<0.04) and 8391 Hz (p<0.04) and SNR average for 4000-8000 Hz in the control (p < 0.04) but not in the study ears.

ITD significantly attenuated hearing loss at 6000 Hz and decreased the outer hair dysfunction in the DPOAE f2 range of 4000-8000 Hz. ITD might have potential in the reduction of Cisplatin-induced hearing loss.

## ANALYSIS OF GENETIC AND NON GENETIC RISK FACTORS FOR CISPLATIN OTOTOXICITY IN PEDIATRIC PATIENTS

Y. Olgun 1, S. Aktaş 2, G. Kırkım 3, D. Çakır Kızmazoğlu 4, A. Pınar Erçetin 2, B. Demir 2, D. İnce 4, K. Mutafoğlu 4, B. Demirağ 5, H. Ellidokuz 6, N. Olgun 4, E. A. Güneri 11 Dokuz Eylül University School of Medicine Department of Otorhinolaryngology, Izmir, Turkey 2 Dokuz Eylül University School Insitute of Oncology Department of Basic Oncology, Izmir, Turkey 3 Dokuz Eylül University School of Medicine Department of Audiology, Izmir, Turkey 4 Dokuz Eylül University School of Medicine Department of Pediatric Oncology, Izmir, Turkey 5 Behçet Uz Children's Hospital Department of Pediatric Oncology, Izmir, Turkey 6 Dokuz Eylül University School of Medicine Department of Biostatistics, Izmir, Turkey

Cisplatin is a neoplastic agent which is widely used for the treatment of various pediatric malignancies. Unfortunately, some side effects like ototoxicity and nephrotoxicity hinders its usage at higher doses. Up to date various risk factors have been accused for cisplatin ototoxicity. The aim of this study is to analyze genetic and non genetic risk factors contributing to cisplatin ototoxicity. Seventy two children who received cisplatin chemotherapy in pediatric oncology department of Dokuz Eylul University School of Medicine and Behcet Uz Children's Hospital were included in this study. Audiological examination of all children were done before and after their treatments by pure tone audiometry, tympanometry and ABR. Brock and Muenster classifications were used as ototoxicity scales. Six single nucleotid polymorphisms including ERCC1, GSTP1 Ala114Val, GSTP1 Ile105Val, Megalin, TPMT, COMT were evaluated by real time PCR. Non genetic factors such as cranial irradiation, high and bolus doses of cisplatin, age, gender, administration of other ototoxic drugs such as furosemide, carboplatin or aminoglycosides were also analysed. By using Chi-square test, all of the risk factors were matched with the two ototoxicity classifications. Risk factors which were found to be significant for ototoxicity by univariate analyses were reevaluated using logistic regression modelling. Of 72 patients, ototoxicity was observed in 24 patients according to Brock and in 30 patients according to Muenster classifications. In univariate analyses, male gender, concurrent use of aminoglycosides and GSTP1 IIe105Val mutant genotype were found to be significantly related with cisplatin ototoxicity (p<0,05). Logistic regression modelling analyses showed that ,male gender (p=0,03) and concurrent use of aminoglycosides (p=0,023) were found to be significantly related with cisplatin ototoxicity. On the other hand, GSTP1 IIe105Val mutant genotype was not found to be significant, but very close to the level of statistical significance (p=0,057). Our findings suggest that, male gender and the concurrent use of aminoglycosides are significant risk factors for cisplatin ototoxicity in pediatric patients. GSTP1 Ile105Val mutant genotype may also seem to be a genetic risk factor in univariate analyses, although not confirmed by multivariate analyses. The importance of GSTP1 Ile105Val genetic polymorphism needs to be evaluated in larger patients series.



7<sup>th</sup> International Meniere's Disease Inner Ear Disorder



# **DEHISCENCE SYNDROME**

OTIC CAPSULE DEHISCENCE SYNDROME: LONGITUDINAL COGNITIVE AND NEUROBEHAVIORAL FUNCTIONAL OUTCOMES BEFORE AND AFTER REPAIR

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Ear and Skull Base Center, Portland, Oregon and the Department of Otolaryngology, University of Pittsburg, Pittsburg, Pennsylvania

Patients with peripheral vestibular dysfunction due to gravitational receptor asymmetries have cognitive dysfunction and assumed neurobehavioral sequelae. Pre- and postoperatively quantitatively measurement in a cohort of patients with superior semicircular canal dehiscence syndrome (SSCDS) symptoms with: superior canal dehiscence (SCD); and otic capsule defects not visualized with imaging and repaired with round window reinforcement (RWR); or both was completed.

Study design: Prospective patient series.

Setting: Tertiary referral center.

Patients: There were 13 adult and 4 pediatric patients with superior semicircular canal dehiscence syndrome (SSCDS) who had completion of neuropsychology test batteries pre- and every 3 months postoperatively. Eight had RWR exclusively, 5 had SCD plugging exclusively, and 4 had both.

Completion of a neuropsychology test battery preoperatively and at 3, 6, 9 and 12 months postoperatively that included: Beck Depression Inventory-II (BDI); Wide Range Intelligence Test (WRIT FSIQ) including average verbal (crystallized intelligence) and visual (fluid intelligence); Wide Range Assessment of Memory and Learning (WRAML), including the four domains of verbal memory, visual memory, attention/concentration and working memory; and Delis-Kaplan Executive Function System (D-KEFS).

Main outcome measures: Quantitative and statistical analysis of their cognitive and neurobehavioral function.

There was a significant decrease in the BDI for all groups. For the WRAML, there was a statistically significant improvement for visual memory and verbal memory for the RWR only and Both groups, but no mean improvement for the SCD only group. All three groups had improvement in the attention/concentration domain. There was no change in working memory for all groups. The IQ scores were unchanged.

Overall there was a marked improvement in cognitive and neurobehavioral function postoperatively. Variability may result from duration of underlying disease before intervention. The initial decrement or delay in performance improvement measured in several patients may represent brain reorganization. Greater longitudinal data and greater subject numbers are necessary to better understand and optimize cognitive recovery.

#### TRANS-MASTOID REPAIR OF SUPERIOR SEMICIRCULAR CANAL DEHISCENCE

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Superior semicircular canal (Sup SC) dehiscence syndrome is a rare condition, causing a variety of auditory and vestibular symptoms. The traditional surgical management is a middle cranial fossa, extradural approach to resurface or plug the superior semicircular canal. Plugging of the canal has been shown to provide better symptom control and this has led to development of a transmastoid approach for plugging of the superior semicircular canal. We present further data supporting the use of the transmastoid approach in preference to the middle fossa approach.

Study design: Retrospective multi-institutional case series

Ten patients with eleven procedures were included in this case series from two tertiary otology institutions. Sup SC dehiscence was confirmed by correlation of clinical symptoms with positive audiometric, VEMP and CT findings. A transmastoid approach was used for plugging of the Sup SC canal. Either a single fenestration was created at the site of dehiscence, or separate fenestrations sited ampullopetal and ampullofugal to the dehiscence.

All patients who underwent this procedure had good symptom control and hearing preservation postoperatively.

In patients with adequate temporal bone pneumatization, the transmastoid approach provides a safe and effective alternative to the middle cranial fossa approach. This series has demonstrated excellent symptom control and preservation of hearing with the transmastoid approach.

## SUPERIOR CANAL DEHISCENCE AND "NEAR DEHISCENCE" SYNDROME: CLINICAL AND INSTRUMENTAL ASPECTS

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Even though superior canal dehiscence syndrome (SCDS) has already been widely studied from a clinical, etiopathogenetic and therapeutic point of view, some diagnostic aspects have yet to be clarified. It is well known that high resolution CT (HRCT) scan tends to overestimate the prevalence of the bony defect requiring the detection of lowered thresholds of air-conducted (AC) VEMPs to confirm the diagnostic suspect. The most recent definition of the so called "near dehiscence syndrome" (NDS), in which an extremely thinned bony roof of the superior canal results in the onset of a symptomatological scenario overlapping SCDS, has allowed to explain most cases of incongruence between imaging analyses and electrophysiological data. Moreover, no univocal explanation to the wide symptomatological and semeiological variability of SCDS has been offered yet. The aim of this paper is to face the diagnostic dilemma offered by the complexity of this two-fold syndrome (SCDS vs NDS) reviewing the clinical and instrumental data and submitting to statistical analyses a subsample of 100 patients (193 ears) selected from a group of 242 patients (114 M, 128 F, mean age 56.8 y, range 8 - 88 y) showing a dehiscence or a an extreme thinning of the superior canal at least from one side at HRCT scans. Firstly, we verified the effectiveness and the diagnostic accuracy of imaging in confirming electrophysiological data, considering the threshold lowering of AC - cervical VEMPs as the gold standard in diagnosing an increased inner-ear admittance due to SCD and offering pathophysiological explanation for those cases of incongruence between results. Secondly, we sought among instrumental set (AC and BC cervical and ocular VEMPs, video head impulse test, audiometric air-bone gap) the test allowing the best diagnostic criteria for "near dehiscence" and the test correlating most significantly with the size of dehiscence in case of SCDS. While mostly all tests can reliably differentiate SCDS from NDS, from this study emerges that ocular VEMPs represent an effective method to detect the "near-dehiscent" condition from the normal cases.

# OCULAR VESTIBULAR EVOKED MYOGENIC POTENTIALS TO HIGH FREQUENCIES SHOW SEMICIRCULAR CANAL DEHISCENCE

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In 26 patients with CT-verified SSCD and in 30 patients with definite Meniere's Disease (MD), to investigate the effect of frequency on the n10 component of the ocular vestibular-evoked myogenic potential (oVEMP n10) evoked by air conducted sound (ACS) and bone conducted vibration (BCV) at the midline forehead at the hairline (Fz). A hand-held Bruel & Kjaer 4810 minishaker provided BCV stimulation was used, using surface EMG electrodes beneath both eyes, to record oVEMP n10. The stimulus ACS and BCV at either Fz or at the vertex of the skull (Cz) were tone bursts ranging from 125 Hz to 8000Hz. 27 healthy subjects were tested in the same paradigm. In response to ACS and Fz BCV from 125 Hz until 8000 Hz in SSCD patients the oVEMP n10 amplitude beneath the contraSSCD eve was substantially and significantly larger than the oVEMP n10 beneath the ipsi SSCD eye. In normals ACS oVEMPs n10 is present and reproducible until 1000 Hz while in SSCD ACS oVEMPs n10 is present up to far higher frequencies (8000 Hz). To Fz BCV oVEMPs n10 is present until 8000 Hz in 23 patients but only to 1000Hz in normals and Meniere's Disease patients . Testing OVEMP frequency tuning with ACS and BCV allows very simple, very fast identification of a probable unilateral SSCD in a manner which is very easy even for senior patients.







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Transmastoid plugging of the superior semicircular canal in superior semicircular canal dehiscence (SSCD) syndrome and the posterior semicircular canal in intractable benign paroxysmal positional vertigo (BPPV) will produce resolution of preoperative symptoms.

Our aim was to gain insight in the effect of plugging on symptom resolution and postoperative bone and air conduction thresholds. We performed a retrospective review on hearing outcomes and postoperative symptoms of 13 patients who underwent transmastoid semicircular canal plugging by two surgeons in a tertiary referral center between October 2008 and December 2014. All patients received systemic corticosteroids during and after surgery. We evaluated air conduction (AC) en bone conduction (BC) pure-tone averages (PTA) of 0.5 kHz, 1 kHz and 2kHZ before and after surgery in nine patients with SSCD syndrome, three patients with intractable BPPV and 1 patient with a major cholesteatoma and complicating mastoid abscess. We also compared symptoms of 9 SSCD patients before and after surgery.

Hearing was preserved in all patients and even improved in 62%. Mean AC PTA improved from 26 dB at baseline to 20 dB postoperative in patients with SSCD syndrome. Mean bone conduction hearing levels remained the same or worsened slightly, this resulted in a mean reduction in air bone gap (ABG) in all frequencies.

The most common symptoms in patients with SSCD syndrome were autophony (9/9), pulsatile tinnitus (7/9), hyperacusis of bone conducted sounds (6/9). Tullio phenomenon (4/9) and pressure-induced vertigo (3/9). Resolution of autophony was achieved in 8 out of 9 patients SSCD patients, resolution of other symptoms was varying.

Opening and plugging of the semicircular canal through a transmastoid approach proves to be safe and effective in preserving or improving hearing. This study also demonstrated symptom relief achieved after surgery in most patients suffering from SSCD.

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# CONTROVERSIAL ASPECTS OF THE CLINICAL STUDIES ON THE USE OF BETAHISTINE IN MENIERE'S DISEASE

#### EPIDEMIOLOGY, STATISTICS AND RESEARCH DESIGN

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#### MD PATIENTS IN THE ACUTE STAGE

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Meniere's Disease (MD) is an idiopathic inner ear disorder characterized by spinning dizziness (lasting from 20' to 24h), fluctuating hearing loss (HL), ear fullness and tinnitus. The natural history of the disease is characterized by variable periods of exacerbation and remission of symptoms, although cochlear symptoms can also be observed among episodes. The hallmark of an acute attack is prolonged vertigo. Each episode of vertigo is characterized by a sudden unheralded intense sensation of movement, most commonly rotation or spinning, lasting 20 minutes to 12 hours.

Because of the brief duration of each attack the clinical examination of a patient with MD is often performed during the inter-critic period and finds no abnormalities. In the few cases where patients have been observed during a crisis appear quite unwell because of the unpleasant sensation of vertigo. They may be sweaty and pale, unable to stand up safely, nauseated and vomiting. They may have an horizontal nystagmus that changes direction as the attack progresses (beating toward the side of the disease at the beginning and after toward the safe hear). Following an attack, patients are left with a sense of "hangover" for a day or two before recovering to a normal function.

Each crisis can be control by the use of vestibular suppressant and antiemetic medication, in association with electrolyte adjustment and rehydration. Because of the nausea and vomit complained by the patient, the more adapt drug and form available should be choice in every single case. Medications can be divided into different classes, including benzodiazepines, antihistamines, anticholinergies and anti-dopaminergics; also calcium channel blockers may be used as vestibular suppressant, although their role in this context hasn't been yet cleared. Moreover, because of the possible autoimmune origin of MD, the use of oral or intratympanic corticosteroids has been also proposed both to reduce the acuity of the crisis and to promote the audio-vestibular recovery. Last but not least is described the use of osmotic diuretics (mannitol, glycerol etc.) administered intravenously. The rationale for their use is based on the supposition that these drugs can alter the fluid balance of inner ear, leading to a depletion of endolymph and a correction of hydrops. All these molecules, administered alone or in combination, constitute a possible treatment during a crisis of MD, although to date there is not consensus and are not available strong evidence about the recommendation of any of these drugs. The method of administration depends on the development of vegetative symptoms and the availability in the formulation of each molecule, so it could be orally, intramuscularly, intravenously or rectally. We underline that, because of the action inhibiting the vestibular compensation of the most of these drugs, their use should be limited to the acute phase and stopped as soon as possible. In this phase a molecule as betahistine, that is described to favor vestibular compensation because of his action against H3 receptors, may play an important role and help the patient to recovery as soon as possible after each episode and come back to his usual activity.

#### MD PATIENTS IN THE INTERCRITIC STAGE

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Principally we believe that more than seventy percent of patients with Meniere's Disease are treated, and their symptoms are controlled by medical treatment. Today's treatment modalities for Meniere's Disease are subjected to the inner ear mechanisms that are being accused for the development of the disease.

Among the conservative and medical treatment modalities, the preferred measures also change due to the geographical locations over the world. In US, during the intercritic stage, re-arrangement of diet by especially restricting salt consumption and coffee as well, and many other measures to regulate the living conditions as well as prescribing diuretics have been the primary concern. For many other countries use of betahistine has been the primary tool to control the symptoms and treat. Currently the dose and duration of use for betahistine for better controlling the disease is in focus by many scientific studies. Autoimmune disorders are speculated to be one of the main factors on the ethiopathogenesis of the disease. The only location where the autoimmune responses take place in the inner ear is the endolymphatic sac. So the endolymphatic sac will remain as a focus of attention on planning the treatment modalities. The endolymph circulation is also one of the main factors being responsible of the hydrops and so the recently treatment attempts also limited themselves on the cellular mechanisms being responsible of endolymph production.

The management of Meniere's Disease resistant to medical treatment has shown great difference during the last ten years. The strong proponents of vestibular neurectomy began changing the tendencies on the management policies of the disease. The intratympanic injections took place of vestibular neurectomies and even sac operations in most instances. In this lecture a short history of controversies on the treatment policies will be mentioned followed by today's management principles and the evidences that they are based will be criticized.

### MD PATIENTS IN THE REHABILITATIVE STAGE

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The aetiology of Menière's disease (MD) is not fully understood even though genetics and environmental factors very likely determine the onset of the disease. MD is a clinical syndrome characterized by episodes of spontaneous vertigo associated with fluctuating hearing loss, tinnitus and aural fullness. Vertigo and dizziness, and their associated neuro-vegetative symptoms and socio-professional consequences, are extremely disabling for MD patients who show increased anxiety and depression. It seems therefore important to stop vertigo quickly in the rehabilitative stage, and to reduce thereafter the frequency of the vertigo attacks and the anxiety level as well. Neuropharmacological treatments, changes in living conditions, and vestibular rehabilitation therapy protocols are the main ways to achieve this goal.

Considering that vertigo is a direct consequence of the asymmetrical discharge of the vestibular nuclei (VN) on both sides, drugs rebalancing the VN activity constitute a first choice. Among these medications are the calcium channel blockers and the drugs interfering with the histaminergic system. Antihistaminics prescribed for few days during the acute stage can substantially reduce the neuro-vegetative signs and vertigo, whereas histaminergic drugs (betahistine) accelerate the recovery process and reduce the frequency of the vertigo attacks. Assuming that endolymphatic hydrops is responsible for MD onset, salt restriction and use of diuretics can be recommended. Finally, vestibular rehabilitation therapy may be useful to prevent anxiety and depression and to help the patients to regain a good quality of life.

The miraculous management of MD patients, which would alleviate definitively vertigo and the fluctuating sensorineural hearing loss, remains to be found. A better understanding of the MD mechanisms should guide the rehabilitation of these patients.





7<sup>th</sup> International Meniere's Disease Inner Far Disord



# **IT GENTAMYCIN TREATMENT**

INTRATYMPANIC GENTAMICIN FOR DEFINITIVE TREATMENT OF MENIERE'S DISEASE: A SERIES OF 105 PATIENTS

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Meniere's Disease is characterized by three major symptoms: vertigo, hearing loss and tinnitus, which may be accompanied by aural fullness. All symptoms are discontinuous, while synchronous, and variable in intensity. Intratympanic application of gentamicin, an ototoxic aminoglycoside, is a relatively new ablative treatment for vertigo in Meniere's Disease.

We treated 105 patients affected by Menière's Disease with one to three doses of 16 mg of intratympanic gentamicin (ITG) distance to a week. Inclusion criteria were unilateral MD, lack of response to hyposodical/hyperhydric diet and diuretics, more than 3 attacks of vertigo/month, absence of neurological disorders and age <70 years.

Vestibular evaluation included a) functional level scale (FLS), that reflects how Menière's disease affects a patient's activities; b) control of vertigo attacks; c) bedside examination, rotatory chair testing and caloric test. Hearing evaluation was performed with pure tone average (PTA).

After 2 years, the difference of FLS values showed a full recovery in 75 patients (70%), substantial recovery in 30 patients (30%) and no limited or insignificant recovery. After 4 years the values were 80%, 11%, 3% and 6% respectively. About the control of vertigo, after 2 years all the patients (100%) reached a complete recovery, while after 4 years 95 patients (91%) reached a complete recovery, and 10 patients (9%) a limited control. Rotatory chair testing showed symmetry ( $<2^\circ$ ) in 70% of patients, mild asymmetry (2-4°) in 20%, moderate asymmetry  $(5^{\circ}-6^{\circ})$  in 10% and no cases of severe asymmetry after 2 years. The values after 4 years were 80%, 17%, 3% and 0% respectively. PTA showed after 2 years improvement of 15 or more dBHL in 21 patients (20%), worsening in 21 patients (20%) (13% anacusis), and no effects in 63 patients (60%). After four years the values were 13%, 68% and 19% respectively (13% anacusis).

Our ITG protocol lays between the classic high-dose and more effective ITG and the more recent and safe low-dose IGT. The first variant works more often (90% of the time), but also is accompanied by far more risk. Injections are generally given every week, up to a total of 4-6; the treatment is stopped when vertigo ensues, indicating that the gentamicin is affecting the inner ear. The low dose method involves using 1-2 injections of gentamicin, waiting a month between injections. This variant stops vertigo 66-80% of the time, with no significant side effects at all.

ITG achieved satisfying outcome in the control of vertigo attacks in patients suffering from unilateral MD, with a very low incidence of hearing deterioration.

#### HEARING LOSS FOLLOWING INTRATYMPANIC GENTAMICIN

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Hearing loss is a well known complication of intratympnic gentamicin. Dozens of studies, using different protocols for instilling the drug into the middle ear since the 1970' have reported, with the incidence of hearing loss ranging from almost none to over 40%. Several reviews have concluded that the exact protocol of delivering the drug is the most important factor, favoring the use titration of delivery, as opposed to fixed protocols, however, patent series are rather limited in size and many of them do not adhere to the reporting criteria according to the AAOL- HNS guidelines.

This presentation will include

- Review the main protocols for instilling gentamicin into the inner ear and their effect on hearing. 1.
- Analyze the data I collected from one of the largest series on the subject from Toronto (2000, 2003) with reference to hearing 2. loss and its risk factors.

## INTRATYMPANIC GENTAMYCIN TREATMENT. HOW TO CONTROL THE THERAPEUTIC EFFECT? HOW TO RESPECT OTOLITH AND COCHLEAR FUNCTIONS?

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Objectives: Describe the method of Controlled Intra-tympanic Gentamycin Treatment (CIGT). Assess and prevent iatrogenic effects. MATERIAL and METHODS : Retrospective study about 297 cases of meniere disease (MD) « Definite MD » (AAO/HNS) from january 2005 to december 2014. During this time period 24 (8.08 %) cases got a CIGT because they showed a high symptomatic grade (4 or 5 AAO/HNS) and a long duration crisis (2 months or more). Before every session, we evaluated Subjective Visual Vertical (SVV), Pure Tone Audiogram (PTA), Air Bicaloric (30/44° Celsius) Reflectivity (ABR). Intratympanic gentamycin administration (1cc and 40 mg) was done for 20 minutes every session. Treatment was stopped when the ABR decreased below 5% or PTA decreased below 15 %. Afterwards, we performed ABR, PTA, Video Head Impulse Test (VHIT), Vestibular Evoked Myogenic Potentials (VEMP) Results: Before the CIGT : Mean age 61.37 years, Sex ratio 16w/8m, mean symptomatic mean grade AAO/HNS 4.7/5, Vertigo Symptom Scale (VSS) 63.91%, Average PTA 60.45 db HL, ABR 71,29% During the CIGT: 4.33 injections on average were necessary to obtain caloric vestibular areflexia (15%) the hearing (function) was surprisingly stable (4 patients / 16.5 %) or even better (17 patients / 71%) after the CIGT with an average PTA of 56.04 dBHL(p>0.01) . The mean residual ABR at the end of the treatment (after 4.33 injections) was 2.33 % After the CIGT (61.62 months on average) : mean symptomatic grade AAO/HNS 1.57/5 (p<0.01), VSS 23.61%(p<0.01), PTA 64.04 dBHL, ABR 8.38%, VHIT gain MD side 0.54 (average value for the 3 canals) and 0.825 healthy side (p<0.001), otolithic reflectivity with VEMPc 86%

Conclusion: It was common to propose a vestibular neurotomy (VN) to a refractory MD with high symptomatic grade and long duration crisis.

Our study shows the efficiency of the therapeutic action of the CIGT (canalar areflexia) and that the iatrogenic effects of the intratympanic gentamycin can be controlled.

The deviation of WS is a predictive parameter of overdosage,

We show a conservation of the cochlear function and comparatively to the VN, the CIGT didn't affect the otolith function.





## LONG TERM VESTIBULAR FUNCTION EVOLUTION AFTER GENTAMYCIN INTRA TYMPANIC INJECTION

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The ototoxic effect of Gentamicin is used as a treatment for intractable Ménière disease with the aim to destroy the vestibular function.

Over the time, the protocol evolved to low doses with objective of hearing preservation and has greatly reduced the dose of Gentamicin injected with apparently a good control of vertigo.

The aim of the study is to evaluate the long term results, after Gentamicin TTI of:

- -Vestibular function by caloric test.
- Control of vertigo.
- Correlations between the two.
- 3/ Material and methods
- Retrospective study of a consecutive series of patients between 2007 and 2012 with intractable Ménière disease (AAOHN 3.1. criteria). 40 patients included among 49 selected.
- We perform a low dose protocol, with one injection of Gentamicin 40 mg/ml (0.3 and 0.6 ml), repeated if necessary between 3.2. 1 and 12 months, depending on clinical vertigo.
- Vestibular function wad assessed by caloric test with bicaloric investigation, and VNG registration. 3.3.
- 3.4. The analysis criteria were: -The vestibular deficit (0 to 100), by three measures: "Def pre" before TTI; "Def max," maximal value of vestibular deficit during the first course of treatment and "Def LT", deficit long term as last value at the end of follow-up. -The variations of vestibular deficit (0% to 100%) between Def LT and Def max; and between Def LT and Def pre.
- 4.1. The mean follow-up is 4, 65 years (2 to 8 years). The control of vertigo at the end of follow-up: 77% class A and 23% class B. Nevertheless, different post TTI disease history has been seen:
- 4.1.1. Group 1: 1 TTI with complete control (N= 15; 37,5%).
- 4.1.2. Group 2: 2 to 4  $\Pi$ I, during one course of treatment with no recurrence (N=13; 32,5%).
- 4.1.3. Group 3: recurrence with new  $\Pi$ , after more than one year of vertigo control (N= 10; 25%).
- Global results of vestibular function for the mean vestibular deficit: Def pre= 50, 3 (SD = 17); Def max= 87, 8 (SD = 13); 4.2. Def LT =85, 1 (SD = 15).
- The mean variation of vestibular deficit is 2,8% between Def LT and Def max and 84% between Def LT and Def pre, traducing 4.3. that vestibular deficit is increased after Gentamicin, and seems to remain stable after long term follow-up.
- 4.4. We analyze also the intra-individual stability of vestibular function, considering the variations between Def LT and Def max classified on 3 situations: no change (< 15%), recovery or aggravation, more than 15% of variations. When the vestibular function recuperates (N = 5; mean 31,9%) the frequency of recurrences increases (60% of cases), whereas when it remains stable N=26, the frequency is only of 26%, and there is no recurrence when there is an aggravation of vestibular function.
- The recurrence cases analysis was done in 10 cases/37, and compared to other cases without recurrence. No difference, in 4.5. mean Def pre, or in mean Def max (86,3/89), but a vestibular recuperation tendency was noted in recurrence group or Def LT (78/87) or Def LT/Def max = 11%/0,2% respectively on recurrence group versus no recurrence group.

At the end of the follow-up study, this group of patients has a complete or substantial control of vertigo, but with different profiles of vertigo evolution.

This seems to be linked with vestibular function and can push us to be more aggressive, in term of number and frequency of TII, when the vestibular function showed a likely recovery vestibular function.

# MONITORING OF CHEMICAL LABYRINTHECTOMY BY GENTAMICIN INJECTION ASSESSED BY VIDEO HEAD IMPULSE TEST AND VEMPS IN PATIENTS SUFFERING FROM MENIERE DISEASE RESISTANT TO MEDICAL THERAPIES

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Chemical labyrinthectomy by intratympanic injection of Gentamicin is an interesting alternative treatment of the vestibular neurotomy for patients suffering from Meniere disease resistant to medical treatment. But how many injections are needed? We sought to answer this by using assessment of vestibular function using both horizontal and vertical video Head Impulse Test (vHIT) of semicircular canal function and cervical and ocular VEMPs tests of saccular and utricular function of patients tested before and after gentamicin injections.

20 patients suffering from Meniere disease had weekly gentamicin injections (80mg/2ml, 1 to 3 injections). They were tested before injections by vHIT, caloric test, cervical and ocular VEMPs, and hearing test. Balance was assessed using Equitest and Wii plus foam. Just before a new injection, canal function was assessed by vHIT in order to follow the VOR decrease and ocular nystagmus was measured using video-nystagmography. Patients were followed longitudinally at 1, 3 and 6 months after the last injection. The necessary number of injections to induce effective unilateral vestibular loss varied between patients: some patients needed only one injection; others needed two or three injections. The measurement of ocular nystagmus with fast phase oriented toward the intact side was not sufficient to decide to stop the injection. Our functional test data gave clear indication about the effect of gentamycin injections with time. VHIT showed a decreased vestibulo-ocular reflex gain in horizontal and vertical canal planes. Ocular VEMPs were also crucial indicators to assess the gentamicin-induced utriculo-ocular dysfunction. In conclusion, monitoring vestibular function using vHIT and VEMPs before each injection allowed us to define specific criteria to detect signs of effective vestibular loss and determine the necessary number of intratympanic injections. None of our patients exhibited acute vertigo during the first one year of follow-up. No hearing loss could be observed even at high frequencies (6000 and 8000 Hz). Therefore, using these tests to monitor the efficacy of chemical labyrinthectomy was a very safe, efficient and noninvasive method to suppress acute vertigo in patients suffering from a cochleo-vestibular hydrops.

# **BPPV**

## SPONTANEOUS INVERSION OF NYSTAGMUS WITHOUT A POSITIONAL CHANGE IN THE HORIZONTAL CANAL VARIANT OF BENIGN PAROXYSMAL POSITIONAL VERTIGO

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We investigated the neuro-otological findings, including nystagmus, and the clinical course of patients with the horizontal canal variant of benign paroxysmal positional vertigo (HC-BPPV), who showed spontaneous inversion of nystagmus without a positional change.

Some patients with HC-BPPV present with spontaneous inversion of nystagmus without a positional change; in other words, biphasic nystagmus sometimes occurs in the same head position during the positional test. In this study, we speculated on the possible mechanism of spontaneous inversion of nystagmus without a positional change. The characteristics of spontaneous inversion of positional nystagmus without a positional change were analyzed in 7 patients with HC-RPPV

All patients were diagnosed as having HC-BPPV. During the positional test, the spontaneous inversion of nystagmus was observed in the same head position in all patients. Spontaneous inversion was observed on both sides in 5 patients, and only on 1 side in 2 patients. All patients presented with geotropic nystagmus in the first phase, and ageotropic nystagmus in the second phase. The coexistence of cupulolithiasis and canalolithiasis appears to be a possible mechanism of the spontaneous inversion of positional nystagmus.





#### EFFECTS OF HEARING DYSFUNCTION IN BPPV PATIENTS

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BPPV is known as the vertigo disease without hearing dysfunction. However, we see some patients with worse hearing in the affected side of BPPV. BPPV is also known to occur in the elderly people. The elderly people may have inner ear dysfunction, because they also have high tone loss on both sides without laterality.

To investigate the effect of hearing dysfunction in the patients with BPPV.

We retrospectively analyzed 258 patients with idiopathic BPPV (i-BPPV) who had not had inner ear dysfunction before the BPPV attack, and 35 patients with secondary BPPV (s-BPPV) who had the BPPV attack after inner ear dysfunction, between January 2011 and December 2013 at the Department of Otolaryngology, Tokyo Medical University hospital. The hearing between the affected side of BPPV and the other was studied.

The i-BPPV patients were divided into 2 groups, one with the hearing with high tone loss (H+) and the other with the hearing without high tone loss (H-). When the sum total of the hearing threshold of high frequency (2, 4 and 8 kHz) was 100 or more, the patient was classified into group H+.

We investigated 1. Age and gender, 2. Averaged hearing level, 3. Laterality of the hearing, 4. Canal type of BPPV, 5. Curing period of BPPV and 6. Recurrence rate of BPPV in i-BPPV and s-BPPV patients.

1. Age and gender

There were 31 male and 56 female, and the averaged ages was 71.9 years old (y.o) in the group H+. There were 53 male, 118 female, and 53.2 y.o. in the group H-. There were 10 male, 25 female, and 62.4 y.o. in the group s-BPPV.

2. Averaged hearing level

> Averaged hearing level in the affected side and the other side were 32.5dB and 30.8dB in the group H+, 15.7dB and 16.1dB in the group H-, and 42.7dB and 32.3dB in the group s-BPPV.

3. Laterality of the hearing

> The hearing was worse by more than 5dB in the affected side of BPPV in the 44.8% of group H+, 33.1% of group H-, and 68.2% of group s-BPPV. Then, the hearing was better by more than 5dB in the affected side of BPPV in the 30.2% of group H+, 33.8% of group H-, and 29.4% of group s-BPPV. These rates were similar in each frequency.

Canal type of BPPV 4

> Posterior semicircular canal type (PSC) was 62.1% in the group H+, 60.9% in the group H-, and 65.7% in the group s-BPPV. Lateral semicircular canal type (LSC) was 29.9%, 35.1% and 22.9%.

5. Curing period of BPPV

The averaged curing period was 15.9 days in the group H+, 12.7 days in the group H-, and 51.6 days in the group s-BPPV.

6. Recurrence rate of BPPV

The recurrence rate of BPPV was 19.5% in the group H+, 16.4% in the group H-, and 14.3% in the group s-BPPV. The high tone loss in i-BPPV patients is due to the aging and not to BPPV. The laterality of the hearing can be associated with the

affected side in i-BPPV patients, but the hearing is not associated with the prognosis of i-BPPV. The hearing dysfunction due to the inner ear disease is associated with the prognosis of BPPV. The hearing dysfunction, including the high tone loss, in BPPV is not associated with the canal type or the curing period of BPPV.

# IMPACT OF CUPULOLITHIASIS ON PATIENTS' WELL BEING

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There are only a small number of studies about benign positional vertigo (BPV) type cupulolithiasis. The study aims to investigate the self-perceived sense of disability in people with BPV type cupulolithiasis and investigate the vestibular symptoms that affect patients and to what extent.

Method: The study consisted of 22 respondents who answered the questionnaires The Dizziness Handicap Inventory (DHI) and The Vertigo Symptom Scale (VSS). The DHI was divided into three components; physical, functional and emotional impact of vertigo. The VSS examined how frequent vertigo related symptoms occurred one year after the diagnosis of BPV type cupulolithiasis. The respondents' points were presented in the form of averages where the biggest troubles and the most frequent symptoms were highlighted and which health problems were the hardest to live with. Results: The study demonstrated a moderate self-perceived sense of disability caused by cupulolithiasis. Patients experienced mainly physical complaints where the greatest physical trouble was that the symptoms increased during rapid head movements. The most frequent symptom was headache or pressure in the head, which occurred more than once per month. Instability was the most difficult symptom to live with.

Conclusion: The study shows a moderate negative outcome in patients with BPV type cupulolithiasis, which was primarily physical.

## NEW THEORY OF BPPV PATHOLOGY "CRISTOLITHIASIS" - OTOCONIA ATTACHED TO THE CRISTA AMPULLARIS

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Nystagmus of BPPV canalolithiasis gradually decreases by repeating positional change (fatigability). On occasion, the nystagmus disappears suddenly by positional change and appears again. Its mechanism seems to be different from the fatigability. We suspect this phenomenon being induced by the otoconia attached to and detached from the base of the crista. We arbitrarily call this "cristolithiasis". The validity of this theory was investigated.

The labyrinths of the bullfrog were used. The membranous labyrinth was cut at the crus commune to create a tiny, 0.5 mm opening. A small piece of otoconia, removed from the sacculus of the other ear, was introduced through this opening into the canal lumen. Experiment 1: The position of the preparation was changed so that the otoconia move back and forth within canal to canal and canal to ampulla. We observed the movement of the otoconia for maximum to ten times. The rates of otoconia attachment to the canal wall and the crista were investigated. Experiment 2: The model of the otoconia attached to the cupula (cupulolithiasis) or the crista (cristolithiasis) was used. These models were given two kinds of stimuli, a. gravity and b. vibration. Experiment 2a (Gravity): The labyrinth preparation was placed so that the cupula-to-crista axis was in the horizontal plane with the canal side in downward position for 30 minutes. The rates of the otoconia detachment from the crista or the cupula were investigated. Experiment 2b (Vibration): Mechanical vibration was applied to the bony labyrinthine capsule of these models using a surgical drill. The time required for otoconial detachment was measured. All experiments were conducted according to the ethical rules for animal experiments at Tokyo Medical University. Experiment 1: No otoconial mass was attached to the canal wall in 6 labyrinth preparations. The otoconial mass was attached to the crista in 5 out of 6 (83.3%) labyrinth preparations. The otoconia were attached more easily to the crista than the canal wall. Experiment 2a (Gravity): In cupulolithiasis models, the otoconial mass was detached within 30 minutes in 2 out of 10 (20%) labyrinth preparations. In cristolithiasis models, the otoconial mass was detached within 30 minutes in 11 out of 14 (78.6%) labyrinth preparations, which was significantly higher than in the cupulolithiasis models (p=0.015). Experiment 2b (Vibration): In the cupulolithiasis models (n=14), the average detachment time was 140.3 seconds. In the cristolithiasis models (n=11), the average detachment time was 25.5 seconds, which was significantly shorter than in the cupulolithiasis models (p=0.0010). The otoconia of cristolithiasis were detached more easily than cupulolithiasis.

The inner wall of the semicircular canal is covered by wall cells with smooth surface. The otoconia of canalolithiasis move along the canal smoothly. On the other hand, the basal portion near the crista has transitional cells, planum semilunatum, and dark cells. The epithelia have microvilli and secretory activity to which the otoconia easily become attached. The attachment is weaker than cupulolithiasis. It is assumed that this attachment and detachment of the otoconia lead to disappearance and return of the nystagmus.





## BENIGN PAROXYSMAL POSITIONAL VERTIGO PREVALENCE IN MENIERE'S DISEASE: IS Meniere's Disease A PREDISPOSING FACTOR?

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Background: Meniere's Disease (MD) is a chronic illness defined as the idiopathic syndrome of endolymphatic hydrops. Benign paroxysmal positional vertigo (BPPV) is a balance disorder and can be the sequela of diverse inner ear impairments. Objectives: The purpose of this study was to investigate the incidence of BPPV in MD patients. Materials and Methods: A total of 39 patients (43 ears) with definite or probable MD (23 female, 13 male; mean age:  $46.4 \pm 9.2$  years) were enrolled in our study. We used the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) criteria plus electrocochleography (ECochG) test results to define the presence of MD and positional and positioning tests to determine the presence of BPPV. Results: Twenty eight of the 43 ears (65.1%) had abnormal ECochG test results. Six out of 39 cases (15.4%) had BPPV in the posterior semicircular canal. There were no cases of BPPV in the lateral or superior semicircular canals. The mean duration of MD was 28.5 months in BPPV group and 13.2 months in the non-BPPV group. Regardless of the age of the patients, there was a significant difference (p = 0.02) between the duration of MD in the two groups. Conclusions: Based on our findings, a longer duration of MD may result in a greater risk of developing BPPV. These findings also suggest that the incidence of BPPV is more affected by the duration of the disease and the condition of the labyrinth than it is by aging. Keywords: Meniere's Disease; Benign Paroxysmal Positional Vertigo; Electrocochleography.

# **IT STEROID TREATMENT**

DEPENDENCE OF HEARING IMPROVEMENT ON THE DOSE OF INTRATYMPANICALLY APPLIED GLUCOCORTICOIDS: A META-ANALYSIS USING MATHEMATICAL SIMULATIONS OF CLINICAL DRUG DELIVERY PROTOCOLS

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To establish optimal local drug delivery protocols for the treatment of patients with idiopathic sudden sensorineural hearing loss (ISSHL). Controlled and uncontrolled studies with intratympanic application of glucocorticoids for ISSHL.

A total of 51 studies with 61 treatment groups between January 2000 and June 2014 were selected based on description of protocols with respect to drug concentration, dosing regimen (i.e. start, number and time intervals of treatment), and outcome parameters sufficiently detailed for analysis with the computer model.

Cochlear drug levels were calculated based on the concentration and volume of glucocorticoids applied, the time the drug remained in the middle ear, and on the specific timing of injections.

A validated computer model of drug dispersion in the inner ear fluids was used to calculate cochlear glucocorticoid drug levels resulting from specific clinical delivery protocols. Dosing in the cochlea and parameters of the delivery protocol were compared with changes of hearing sensitivity and final outcome. Time courses were quantified in terms of the maximum concentration (Cmax) and the area under the curve (AUC) of the drug at specific cochlear locations.

There was no influence of applied drug concentration, application time, number of injections, interval between injections, duration of treatment, total local dose (quantified as AUC or Cmax) on outcome. For "rescue therapy" situations there appeared to be no need to start within two month from onset of ISSHL. This calls into question the importance of the choice of drug and application protocol, and perhaps the effectiveness on intratympanic glucocorticoid therapy for ISSHL in general.

Change in pure tone average (PTA) might not be an adequate outcome parameter to assess effectiveness of the intervention, since it appears to depend on initial hearing loss. Final PTA might be used as an alternative parameter when comparing different clinical reports. Further efforts should be made towards standardization of outcome parameters and publication of outcomes in individual patients in clinical studies with interventions to improve hearing.

## GLUCOCORTICOIDS STIMULATE ENDOLYMPHATIC WATER REABSORPTION IN INNER EAR

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Meniere's Disease, clinically characterized by fluctuating, recurrent, and invalidating vertigo, hearing loss, and tinnitus, is linked to an increase in endolymph volume, the so-called endolymphatic hydrops. Since dysregulation of water transport could account for the generation of this hydrops, we investigated the role of aguaporin 3 (AQP3) in water transport into endolymph, the K-rich, hyperosmotic fluid that bathes the apical ciliated membrane of sensory cells, and we studied the regulatory effect of dexamethasone upon AQP3 expression and water fluxes. The different AQP subtypes were identified in inner ear by RT-PCR. AQP3 was localized in human utricle and mouse inner ear by immunohistochemistry, and confocal microscopy. Unidirectional transpithelial water fluxes were studied by means of 3H2O transport in murine EC5v vestibular cells cultured on filters, treated or not with dexamethasone (10-7 M). The stimulatory effect of dexamethasone upon AQP3 expression was assessed in EC5v cells and in vivo in mice. AQP3 was unambiguously detected in human utricle, and was highly expressed in both endolymph secretory structures of the mouse inner ear, and EC5v cells. We demonstrated that water reabsorption, from the apical (endolymphatic) to the basolateral (perilymphatic) compartments, was stimulated by dexamethasone in EC5v cells. This was accompanied by a glucocorticoid-dependent increase in AQP3 expression at both mRNA and protein level, presumably through glucocorticoid receptor-mediated AQP3 transcriptional activation. We show for the first time that glucocorticoids enhance AQP3 expression in human inner ear, and stimulate endolymphatic water reabsorption. These findings should encourage further clinical trials evaluating glucocorticoids efficacy in Meniere's Disease.

## COMPARISON OF INTRA-TYMPANIC STEROID THERAPY PROTOCOLS FOR MENIERE'S DISEASE BETWEEN CENTERS IN THREE MEDITERRANEAN COUNTRIES

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Intra- tympanic steroids have become the treatment of choice for Meniere's patients who do not respond to conservative therapy, which includes low salt diet, betahistine and diuretics. The rational of the treatment is based on the theory that Meniere's is an immune mediated disorder. The treatment is aimed to reduce the number and severity of the vertiginous attacks and ameliorate the associated hearing loss and tinnitus. Studies have shown the efficacy of this treatment but do not refer to a specific uniform protocol. There are numerous protocols in use among centers around the world. We aim to describe the different protocols used in three tertiary centers in three Mediterranean countries (Slovenia, Turkey and Israel) in terms of the mode of delivery, dosage and frequency of applications. The delivery method in Ljubljana, Slovenia (SB) is via a myringotomy conducted over the round window with a circle knife. In addition, a small anterior hole is made for pressure relief. In Eskisehir, Turkey (AI) the hole is made by a 27 gauge dental needle and in Jerusalem, Israel (RP) using a laser myringotomy. The diameter of the myringotomy is 2.0 mm, shown to stay patent for approximately one week. With respect to dosage, in Slovenia 1.5 ml solution of 24mg/1ml dexamethasone is used and in Turkey and Israel, 4 mg/ml at 1 and 0.5 ml respectively. In Eskisehir and Ljubljana injections are given every other day. While in Eskisehir only 3-5 injections are given, in Ljubljana injections are given until symptoms improve. In Jerusalem daily injections are given and in case improvement is seen in the later injections, treatments are continued once a day. In Israel the patient stays on the bed with the head oppositely tilted for 15 minutes, in Turkey for 30-45 minutes and in Slovenia for 2-3 hours.

The wide variability in treatment protocols of intra-tympanic steroids for Meniere's Disease is demonstrated. We recommend that the treatment results should be compared and a uniform protocol determined.


#### EVALUATION OF LONG TERM EFFECT OF INTRATYMPANIC DEXAMETHOSONE THERAPY (ITD) IN MENIERE'S DISEASE (MD)

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Intratympanic dexamethason therapie (ITD) is documented to reduce vertigo attacks in patients with MD by 80-90% in the literature. Between 2006 and 2011 we treated 48 patients with definite MD (AAO-HNS) with 1 to 3 series of intratympanic dexamethason injections. The success rate of reduction of vertigo attacks by at least 60% following ITD was 94% after 1 year and 80% after 5 years. The aim of this study was to assess the course of MD in the patients treated with ITD in 2006 four years after the end of our former study. Retrospective chart review of the patients (n= 48) that participated in the former study (2006-2011) and assessment the current activity of MD and the quality of life by structured questionnaires.

We obtain two groups of patients: The first group reveals low activity of MD without further interventions necessary ("cure"). The second group ("palliation") shows high activity of MD with two subsequent subgroups according to their further interventions (A: ITD; B:intratympanic gentamycin (ITG)). ITN allow Long-term cure in the majority of patients, provides the option for further injections "as needed" or allows a subsequent change to more destructive treatment.

#### INTRA-TYMPANIC DEXAMETHASONE IN THE TREATMENT OF DISABLING VERTIGO IN MENIERE DISEASE

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The purpose of this study is to determine if intratympanic dexamethasone is effective in controlling vertigo in Meniere Disease. Patients who underwent intratympanic dexamethasone therapy using the Microwick technique between May 2011 and May 2013 were evaluated. The effect of therapy on the incidence of vertigo, fluctuating hearing loss, fullness and pressure in the ear, and tinnitus was analysed. The number and percentage of patients who had to undergo intratympanic gentamicin therapy due to failure of the steroid therapy will be presented. The technique, results , and statistical analysis will be presented.

Intratympanic dexamethasone does not appear to be successful in controlling the recurrent vertigo attacks in our Meniere Disease population.

## **CLINICAL ISSUES 1**

IDIOPATHIC ACUTE LABYRINTHINE DISEASES AND MENIERE DISEASE: THE NECESSITY OF A MULTIDISCIPLINARY APPROACH

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In the past years, our group has outlined the importance of hemodynamic imbalances of both organic and functional origin as a causal factor of labyrinthine affections with acute onset. Actually, a series of observations has witnessed the influence of a temporary lack of perfusion, possibly due to an abrupt lowering of blood pressure followed by an abnormal vasoconstriction, in the genesis of such damages. This pathogenic model fits with the anatomic and functional characteristic of the inner ear that is fed by a terminal type circulation, and therefore is more easily prone to transient ischemia; in our opinion, it could be considered as a possible pathogenic factor in a number of unexplained labyrinthine affections including Meniere disease. Starting from the alterations produced in a terminal and highly energy requiring organ as the inner ear by a more or less long-lasting ischemia, the damage could result in an impairment related to the duration of the lack of perfusion: hence tinnitus, vertigo episodes, reversible sudden hearing loss, hydrops and severe non -reversible sudden hearing loss could be imagined as deriving from a common causal factor. Due to the variability of factors able to interfere with inner ear perfusion, especially concerning autonomic regulation and cardiocirculatory conditions, a diagnostic and therapeutic approach seems mandatory: when taking into account these factors a more accurate overall clinical picture can be disposable, thus permitting to avoid inappropriate therapeutic choices.

### MENIERES' DISEASE SYMPTOMATOLOGY IN RELATION TO THE 1995 AAO-HNS

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Meniere's Disease (MD) is a complex progressive disorder of the inner ear characterized by sensorineural hearing loss, episodic vertigo, tinnitus and aural fullness. MD diagnosis is essentially based on clinical history and specific tests are usually not required. In 1995 the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology - Head and neck Surgery published the guidelines for MD diagnosis and classified it in certain, definite, probable and possible. The study group consisted of 384 consecutive subjects affected by MD according to the AAO-HNS 1995 guidelines. In each case we collected an exhaustive anamnesis regarding all the aspects of the disease and we measured the pure-tone audiometric threshold. Of the overall sample, 228 subjects (59%) were affected by definite MD, 30 (8%) by probable MD and 126 (33%) by possible MD. In the latter group of 126 subjects, 90 (73%) had only hearing loss and 36 (27%) only vertigo. Age at the beginning of the disease was not different between probable and possible groups, while subjects with definite MD were older with longer duration of the disease. Disability level was lesser in the possible forms. Among the 228 definite forms, MD appeared with both vertigo and hearing loss together (temporal delay less than 24 hours) in 79 cases (35%), with hearing loss alone in 96 cases (42%) and with vertigo alone in 53 cases (23%). PTA mean threshold at 0.5-1-2-3 kHz at the first control in the 228 cases of definite MD was worse than in the 90 subjects affected by possible MD with just cochlear involvement. In conclusion definite form represents the most common form of MD at diagnosis and comprises the most disabling cases. However, in the majority of cases, the disease starts either with cochlear or vestibular symptoms (possible MD) and evolves in definite usually within 5 years.

### GLUTEN SENSITIVITY AND MENIERE'S DISEASE

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A possible relationship between gluten sensitivity (GS) and Meniere's Disease (MD) has already been reported in literature. Many authors are currently studying the humoral immune responses (biomarkers) to all wheat antigens and peptides in patients with diseases that are related to wheat ingestion. The aim of this study was to assess the humoral immune responses to wheat antigens, and in particular, IgG and IgA antibody production against all of the antigens and peptides associated with gliadin in patients with MD with or without GS (MD-GS+ and MD-GS-).

We used the sera of 28 patients with MD, 14 of whom proved to be sensitive to gliadin at skin prick testing and 14 whose results were negative. The serum of 100 healthy patients was used as the control in order to establish the normal range for the biomarkers tested. There were no significant differences between MD-GS+ and MD-GS- for all of the biomarkers with the exception of IgG anti-transglutaminase 3. (p < 0.005)

Our results confirm the importance of the delayed response to skin prick testing in identifying patients with GS in MD, as previously reported in literature.

The increase of IgG anti Transglutaminase 3 antibodies requires further study in order to define whether it is purely incidental.



#### THE SOCIAL IMPACT OF MENIERE'S DISEASE: THE ROLE OF DIFFERENT TREATMENT STRATEGIES

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The social and work life impact of dizziness on patients suffering from unilateral definite Menière's disease was assessed by the validated 'Social life & Work Impact of Dizziness questionnaire' (SWID), which has been already adopted to evaluate the social impact of dizziness in two different countries (1). SWID represented the main outcome measure associated with the number of vertigo attacks and the perceived deterioration of hearing in the last six months. The questionnaire was administered to each patient by e-mail. All subjects reported also their last pure tone average score and the treatment they underwent in the last 6 months. More than 200 patients completed the questionnaire. The mean number of days off work attributed to the dizziness in the previous 6 months was more than 7 days. Social life was disrupted in more than 50% of all patients. Statistically significant differences in the social and work impact of the disease were observed among groups treated with different strategies (betahistine, diuretics, steroids, intratympanic gentamicin, etc). The social and work life impact of Menière's disease is very high.

#### THE NATURAL HISTORY OF MENIERE'S DISEASE: A SYSTEMATIC REVIEW

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Meniere's is a commonly encountered condition in otological medicine and while many have sort effective treatment strategies the underlying pathophysiological basis is poorly understood. The natural history of the disease varies greatly and while some patients will develop the classic triad of hearing loss, tinnitus, vertigo others will have a less reliable course. We aim to report on the course of the disease in untreated patients by means of a epidemiological systematic review.

Eight literature platforms including PubMed, Science Direct and EBSCO Host underwent a systematic search (of English language, peer-review journals) using the terms: Meniere's AND natural history OR waiting OR wait\* OR waiting-list OR watchful OR observation OR control group. The review was registered on the PROSPORO review database. Primary outcomes (with respect to vertigo severity) frequency, hearing los, tinnitus and quality of life) of patients with Meniere's disease (Grade I AAO-HNS diagnosis) undergoing either no active treatment, watchful waiting or on a waiting list for treatment are reported.

2256 papers were identified and through initial inclusion criteria, 244 papers were reviewed with reporting in line with the PRISMA statement. The results of the review will be reported according to the classic triad of Meniere's symptoms and as such a meta-analysis for each measure will be considered.

This study will generate the largest body of research regarding the natural history of Meniere's. The volume of research located in the systematic search is considerable and the results will be of interest to fellow researchers and those who counsel and treat patients with Meniere's disease.

COI: Mr John Phillips is the Chief Investigator for the UK OTO-104 clinical trial. John Phillips' attendance to this symposium has been supported by Otonomy.

#### HIGH FREQUENCY DEAFNESS WITH VESTIBULAR EPISODIC SYNDROME

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and sectorial. Its etiology is still not fully understood, but the endolymphatic hydrops is considered as the morphological correlate for the symptoms, such as hearing loss fluctuation, tinnitus, aural fullness and vertigo episodes . However, many authors have pointed out that the natural history of the disease is not always homogeneous, being relatively common, a non-classical evolution of the syndrome.

patients with high frequency deafness with vestibular episodic syndrome (HIVES) Methods: We present a population of 16 patients with recurrent spontaneous vertigo associated with tinnitus, aural fullness and high frequency hearing loss. and compare with a cohort of 30 patients with Definite MD and low frequency auditory impairment. Both cohorts have been fully studied by complete neuro-otological examination, caloric tests, cervical and ocular VEMPs, and extratympanic electrocochleography.

AP ratio or area results, didn't show any significant difference between MD and HIVES group. Both groups have a similar clinical and vestibular presentation. Based on the results of the electrocochleography, both groups of patients share the same pathophysiological basis, the endolymphatic hydrops.

## **CLINICAL ISSUES 2**

### VESTIBULAR IMPLANT, A NEW APPROACH TO BILATERAL VESTIBULAR DISFUNCTION

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Vertigo of vestibular origin has a prevalence of 5% and responds poorly to current treatments. this value rises to 38% in the elderly and increases the risk of falls and the consequent permanent disability, health costs and even death. 12-14 million people worldwide would require a vestibular implant.

Current devices detect cephalic angular velocities and stimulate the semicircular canals. However they do not code vertical and horizontal accelerations, used to sense gravitational forces, keep a stand up position and restore a sense of self-position by the saccule and utricle. We present a project that will electrically emulate linear accelerations reproduced in these organs. Thus, the objectives are:1) to study vestibular pathways, 2) to analize vestibular neural response to electrical stimulation and 3) to restore the sense of linear accelerations. Finally, the project will offer a two-way exchange with inertial system technology, using what has already been discovered and returning innovative bioinspired solutions.



- Aims and Introduction: The pathophysiological basis of Meniere's disease (MD) is endolymphatic hydrops, which is supposedly progressive
- Involvement of the high frequencies associated with recurrent vertigo is a not characteristic finding of MD. We aim to study an group of
- **Results:** We found no significant differences between the results of different vestibular tests in both cohorts. The Electrocochleography SP/



# MENIERE'S DISEASE: WHAT CAN WE LEARN FROM VESTIBULAR IMPLANTS?

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We have placed a prototype vestibular implant in four human subjects with uncontrolled Meniere's Disease who were candidates for labyrinthectomy. The semicircular canals were implanted with a 150 micron diameter array using a "soft-surgical" approach via a ~200 micron labyrinthotomy. Despite preserving hearing and vestibular function in numerous normal rhesus monkeys with the same surgery and device, hearing and vestibular function was lost in all four Meniere's patients. They behaved clinically as if they had undergone a labyrinthectomy except there was far less postoperative vertigo than is typical in a surgical labyrinthectomy. CT in one subject confirms electrodes near all three ampullae. These cases strongly suggest that the Meniere's ear is more susceptible to surgical trauma than a healthy ear consistent with prior observations after stapes surgery, and a published series of accidental posterior canal fenestrations in retrolabyrnthine vestibular nerve section. We have also observed fluctuating responsiveness of the vestibular nerve to electrical stimulation consistent with prior observations of fluctuating speech discrimination in cochlear implant patients with Meniere's Disease. Lastly, one of our subjects was able to modulate the intensity of a Meniere's attack using his takehome stimulator. When stimulating at a current level that evoked vertigo comparable to an attack when no attack was present, he was able to completely suppress the vertigo during an attack. This suggests that at least for this individual, this attack was due to a sudden decline in vestibular nerve firing consistent with one theory of Meniere's pathophysiology.

#### SUBJECTIVE VISUAL VERTICAL IN BILATERAL VESTIBULAR LOSS ROLE OF PROPRIOCEPTION

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Subjective Visual Vertical is a routine test assessing the otolithic function. The participation of proprioceptive input in SW is probably significant but unclear. In order to evaluate this participation, we aimed to study WS in patients with bilateral vestibular loss and different body and neck tilts.

This prospective study included 22 patients with idiopathic bilateral vestibular loss (mean age : 58, sex ratio : 1.2) and 30 adult controls (mean age : 51, sex ratio: 1.3). SW was measured by asking the patient to place vertically a red line on a screen using a remote control. Deviation from vertical was measured in degrees (negative values to the left and positive to the right). The patient was seated on a tiltable seat (TRV seat, Apt, France). SVV was measured in 7 body positions: vertical, head and body tilted 12° to right, then 24°, and then body tilted at 24° with the head upright, subsequently same positions were tested on the left. In each position, SW was measured 6 times.

At vertical position, no difference in SW was observed between vestibular loss and controls  $(-0.2^{\circ} + 1.05 \text{ versus } -0.1^{\circ} + 1.98 \text{ vertical position})$ respectively, unpaired t-test). However, patients with vestibular loss were more sensitive to body tilt (-8.5°  $\pm$  4.64 for vestibular loss versus 0  $\pm$  3.26 for control at 24° body and head tilt to the left, p<0.01, unpaired t-test). Placing the head upright while the body was still tilted significantly reduced this difference suggesting that cervical entries participate in SW. Similar results were observed on the right.

Not only otolithic function but also proprioceptive entries especially cervical sensors participate in SW.

#### SUBJECTIVE VISUAL VERTICAL AND HORIZONTAL IN THE INDIAN POPULATION

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#### To determine the normative values for static and dynamic subjective visual vertical and horizontal (SVV & SVH) in a group of Indian volunteers

The perception of gravitational vertical/horizontal, which is also called true vertical/horizontal, can be assessed by asking an individual either to adjust his/her body position to the vertical/horizontal (postural vertical/horizontal) or to adjust a computer simulated light bar to horizontal or vertical. This can be done under static and dynamic conditions. SVV/SVH is a valid vestibular test that can be used to identify dysfunction in the otolithic pathway which consists of both central and peripheral vestibular system. The test measures the deviations of the perceived vertical from the true vertical which is measured in degrees and this capacity depends on the integrity of visual and vestibular pathway(in specific the utricular pathway) in the brainstem. Hospital based prospective cross sectional study of a group of normal adults After clearance from the institutional research board eighty two volunteers stratified into two groups (20-40, 41-60years) were recruited for the study. Any person with history of vertigo, imbalance, otological complaints (hearing loss/tinnitus/ear discharge/ earache/ear trauma), persistent headache, history of head-trauma, use of ototoxic drugs, prior ENT surgeries, co- morbid illnesses were excluded from the study.

The SW and SVH angles were measured under static and dynamic conditions. This was done by using software from the SW equipment (MUS\_VS-V1.3.2.Rev B) Synapsis Company-France). Six readings each were taken for SVV and SVH in both static and dynamic situations.

Mean values of (1.4+/-0.68) degrees static SW for females, (1.58+/-0.71) degrees static SW for males, (1.82+/-0.64) degrees dynamic SVV for females, (2.04+/-0.65) degrees dynamic SVV for males, (1.63+/-0.76) degrees static SVH for females, (1.65+/-0.84) degrees static SVH for males, (1.80+/-0.60) degrees dynamic SVH for females and (2.1+/-0.86) degrees SVH for males were obtained. There was no significant difference between the sexes and the two age groups. This is the only study in the Indian population and the normative data obtained in this study can serve as reference for future studies and vestibular testing especially in those suffering from chronic vertigo and suspected to have otolithic pathway abnormalities.

#### SELECTIVE WINDOW APPLICATION OF GENTAMYCIN IN MENIERE'S DISEASE

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The purpose of the study is to prevent hearing loss when using IT gentamycin for intractable Meniere's Disease. Ten patients who had definite Meniere's Disease and did not benefit from medical treatment were selected for the study. All had completed vestibular tests and MRI for differential diagnosis. Exploratory tympanotomy were conducted under local anesthesia. The dexamethasone soaked gelatin sponges were applied to the round window and gentamycin soaked gelatin sponges were applied to oval window. The average hearing level in low tones (250, 500, 1000, 2000 Hz) was 50.5±7.7 dB before treatment and 51.2±6.8 dB after treatment. The average hearing level in high tones (4000, 6000, 8000 Hz) was 42.2±19.2 dB before treatment and 47.4±19.1 dB after treatment. The average caloric weakness was  $34.3\pm24.3$  before and  $45.3\pm32.7$  after the application. Two patients have recurrence of vertigo attack in one year of follow up. They continued with Intratympanic gentamycin injection. The use of dexamethasone and gentamycin for different windows in the middle ear is safe and effective method for Meniere's Disease in the short term. Application of dexamethasone protects not only the hearing cells but vestibular cells also.





#### IMPROVING DIAGNOSTICS IN PATIENTS WITH VESTIBULAR PAROXYSMIA TO TREAT THEM IN AN EARLIER PHASE OF ILLNESS

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Vestibular paroxysmia (VP) is defined as short vertiginous spells frequently dependent on head position with an underlying hypothesis that there is a neurovascular conflict (NVC) with the VIII cranial nerve. Although the syndrome was first described more than 30 years ago by Jannetta, there is still a need for more specific diagnostic criteria to make an early diagnosis and treat patients in an early stage of illness.

A study was performed on 18 patients with complaints of vertigo, a NVC on MRI and improvement of symptoms by treatment with carbamazepine or oxcarbazepine. Anamnestic and clinical results were examined retrospectively to determine significant similarities among these patients.

In this study 55 % of the VP patients complained of lightheadedness, while 44 % experienced dizziness and 39 % were unstable. A smaller group of 33 % experienced rotational sensations as well as a drunken feeling. The most common accompanying symptoms were cervical pain (78 %), hearing loss (55%), tinnitus (61%), headache (55%) and aural fullness (38%). The symptoms occurred daily in 81 % of the patients lasting seconds or minutes (71%) often described by the patient as a continuous burden with short episodes of vertiginous spells. The symptoms were triggered by positional changes (78%), specifically by head movement in 50% and only 27 % by rolling over in bed. Clinical examination showed a persistent non-BPPV type nystagmus (71 %). The Chavda classification was used to specify the anatomy of the NVC. There was no correlation found between audiometry, ENG and the type of loop. Several other diagnoses were made which led to a mean duration of 16 months and a maximum of 60 months before efficient treatment for VP.

A combination of anamnestic criteria, clinical examination and imaging is necessary to diagnose VP and more importantly to differentiate it easily from other vestibular pathologies as Meniere's Disease, BPPV and vestibular migraine.

#### UNILATERAL MENIERE DISEASE WITH BILATERAL HEARING LOSS

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When conventional treatment for Meniere's Disease fails, intratympanic gentamicin is considered to be an effective treatment in vertigo control. Gentamicin is an aminoglycoside with ototoxic effect. To our knowledge no previous study has considered the ototoxic effect in the untreated ear, which is one of the questions asked in this study. Our method was to evaluate hearing level gathered from patients pre-treatment, one month and two years post-treatment. Tinnitus related questionnaires were analyzed from patients pre treatment and at the long time follow up. A total of 36 patients were included in this study.

Median pure tone average (PTA) was 57,5 dBHL pre-treatment on with the Meniere affected side. One-month post treatment PTA was 65,6 dBHL and two years after PTA was 64,7 dBHL. The difference was not significant. More instillations seem to relate to higher PTA's. The ototoxic effect had a significant impact on the frequencies 3,4,6,8 kHz. The highest impact is on 6kHz with a median decrease in -10 dBHL. Three patients experienced significant hearing improvement; five patients became deaf post treatment, seven patients got significantly worsened hearing and fifteen patients had no significant change in PTA post treatment. Gentamicin had no impact on the untreated ear after one month. After the follow up period of two years, median for change in hearing level before and after treatment shows decrease in 5 dB on the frequencies 4 and 6 KHZ. According to VAS-results, 41% of the patients experienced an improvement on their tinnitus.

Conclusion: ITG is an effective treatment method for intractable unilateral Meniere with unpredictable hearing outcomes. The ototoxic effect is significant in high frequencies on treated ear after one month. Untreated ear shows a tendency for worsening in in high frequency hearing levels during the following up period of two years.

#### THE RELATIONSHIP BETWEEN THE CEREBROSPINAL FLUIDS AND PERILYMPH. NEW FINDINGS IN MRI AFTER INTRATIMPANIC ADMINISTRATION OF GADOLINIUM

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In Meniere disease hydrops is the necessary condition but it does not explain all clinical features, including the progression of the hearing loss and the recurrence of vertigo. The perilymph and endolymph, the two liquids in the inner ear, and their exchanges are still being studied and if we know a lot of their physical and chemical properties we know little of their dynamics inside the ear. In literature, all papers about the inner ear liquids, were conducted on mice in which the internal ear properties are notoriously different than in human. In particular, the production and resorption of perilymph and endolymph, as well as their endocochlear flow and the role of the cochlear aqueduct are still under study. Recently the radiological investigations with MRI 3 Tesla before and after administration of endotympanic Gadolinium showed a new and completely unexpected feature of perilymph. In 100% of patients with Meniere disease (MdM) the contrast is eliminated in the cerebrospinal fluid (CSF) not through of the cochlear aqueduct but through the internal auditory canal (IAC). This finding leads to new pathogenetic hypotheses in which the role of the CSF could assume greater importance. We reported our experience of 23 patients with defined MdM, according to the criteria of the American Academy, evaluated with 3 tesla MRI with administration of gadodiamide by trans-tympanic injection. In all these patients the gadodiamide was not observed in the cochlear agueduct and was eliminated through the bottom of IAC. This findings demonstrated the relationship between CSF and perilymph in Meniere disease. The possibility that changes in pressure of the CSF could be transmitted to the perilymph, already highlighted in the literature, are discussed.

#### A COMPARISON OF NEUROTOLOGICAL AND PSYCHOMETRIC TEST RESULTS IN MÉNIÈRE'S DISEASE AND PHOBIC POSTURAL VERTIGO

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3 Ministry of Welfare of the Republic of Latvia, clinical psychologist, Riga, Latvia The aim of this study was to analyze relationship between neurotological and psychometric test results in patients with Meniere's Disease (MD), phobic postural vertigo (PPV) and control group in an interdisciplinary prospective study. MD is a diagnosis requiring expert clinical judgement. There is no specific diagnostic test, and many patients meet some but not all of the diagnostic criteria. Several reports suggest a psychosomatic basis for MD. Patients were divided into two study groups: organic disorders caused by MD and psychogenic vertigo caused by PPV (n=31 and 31; age range 23-77 and 26-76 years; mean age 47.48 and 49.26 years; median duration of the disease 3.9 and 3.9 years respectively). Control group (n=31; age range 20-65 years; mean age 38.58 years) presented no ENT disorders or any severe comorbidity. Neurotological diagnostic procedures included videonystagmography (VNG) with caloric testing and pure tone audiometry (PTA) were performed. Patients were asked to fill out self-rated scales: the Dizziness Handicap Inventory (DHI), the Hospital Anxiety and Depression Scale (HADS) and the Beck Depression Inventory (BDI). Results: Patients with MD (45.16%) had pathological test values on caloric irrigation. Patients with PPV and control group showed normal parameters for vestibular testing. Both study groups and control group had pathological values for psychometric measures. Of MD patients, there was weak correlation between the caloric responses and anxiety symptoms (p<0.05). Of PPV and control group, there was weak correlation between the caloric responses and depression symptoms (p<0.05). MD patients' median PTA threshold was 45 dB on affected ear. Patients with PPV and control group PTA was in the normal range of hearing. Correlation between the PTA and other neurotological and psychometric test results was medium close or weak in PPV and control group while in MD group no correlation with any of test results observed (p<0.05). Most of patients had moderate and severe vertigo induced handicap in both MD and PPV study groups 77.42% and 74.19% respectively. There was medium close correlation between the vertigo induced handicap and depression in both study groups and weak correlation in control group (p<0.05). The correlation between the vertigo induced handicap and anxiety was weak in both study groups (p<0.05). The correlation between the vertigo induced handicap and caloric responses was weak in control group (p<0.05). Patients of MD, PPV and control group showed on scales 67.74%, 64.52% and 32.26% anxiety, 74.19%, 70.97% and 16.13% depression respectively. The correlation between the anxiety and depression subscales was medium close in all groups (p<0.05). Conclusions: Results of neurotological diagnostic procedures included VNG with caloric testing and PTA showed weak or no correlation with other measurements in both study groups and control group. Mild to severe anxiety and depression showed about 2/3 of MD and PPV patients. The correlation between the depression and anxiety subscales of the HADS was medium close, which illustrates the frequent coincidence of symptoms of anxiety and depression in both study groups and control group. Thus, comparison among the study groups with any of the above mentioned diagnostic methods were not differentiated patients with MD. The possible difference of organic and psychogenic vertigo syndromes could be valuable in the personality multifactorial evaluation.



7<sup>th</sup> International Meniere's Disease **Inner Ear Disorders** 



## **CLINICAL ISSUES 3**

#### EHEALTH IN MENIERE'S DISORDER IMPROVES QUALITY OF LIFE WHEN MEDICAL THERAPY IS NOT ENOUGH

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Medical therapy tries to heal Meniere's disorder by resolving vertigo, gait problems and hearing loss, but very often the patients have problems and restrictions that reduce the quality of life. Web-based peer support can challenge these problems by being personfocused and available. We have created a peer support program for Menière's disorder (MD) that uses data base resources, applies artificial intelligence in decision making, and has a user-centered approach in determining the impact of the disorder and in the patient empowering process. Methods: Data was retrieved from 740 cases of MD to develop the program. The program uses pattern recognition in the diagnosis of MD. The impact of MD is assessed by ICF-based structured questions. Personal data on quality of life, personal traits, complaints, and attitude are collected interactively. The Norton-Kaplan model is applied to construct a strategic person-focused approach. By working on critical success factors, short term goals are then pursued. Results: The peer-support program comprises the following elements: It first assesses the diagnosis and individual participant's disorder profile. Thereafter it interactively determines the impact caused by the disorder using ICF classification, evaluates personal traits and attitudes towards the disorder, and identifies positive aspects. The eligibility of the subject to enter the program is based on their diagnosis and quality of life score. The inference engine uses a database to compare the impact of the complaints, personal traits and attitudes with 50 referents. In the therapeutic component, the participant defines vision, time frame, inspects confounding factors, determines goals, establishes a strategy and starts to work on the three most important ICF-based problems caused by the disorder. Interactively with the person, the program guides them to find solutions that minimize their restrictions. The program utilizes collaboration with significant others and enhances positive thinking. To assist the person to cope, reference data on coping strategy are retrieved from the database. In the outcome analysis, several measures including quality of life, post traumatic growth factor index and personal satisfaction are used. The program provides a hard copy of personal complaints, problems, strategy, attitude, goals and outcome measures. The information package contains pdf-files of major complaints, 240 animated slides and 12 video case histories. Among 235 persons participating in the data collection 75 % found the program guestion useful or very useful in supporting their life with Meniere's disorder. Those with acute disease regained more information than those with chronic disorder. Among 31 participants passing the whole program the general health related quality of life (EQ-5D) improved by 14%.

We have created a web-based peer-support system that is user-centered, able to classify the characteristics, profile the impact of the disorder, assist in decision making, and interact with the individual participant. The program contains a large database on the complaints and impact of MD. The modified Kaplan-Norton model is used to establish a personal strategy that empowers the participant and improves coping with the disorde.

### ALTERNATIVE MEDICINE AND NON-INVASIVE THERAPIES FOR THE TREATMENT OF MENIERE'S DISEASE

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known for its

ascribes

elements. The management of Meniere's Disease is controversial, consequently its treatment is currently empirical and the therapies are aimed at controlling the symptoms.

cope with this disease.

treatment of anxiety appear to be helpful. Nutrition education can improve the results of medical treatment: dietary protocols often include low-sodium diet and reduction of caffeine, nicotine, and carbohydrates intake. Some studies have assessed the impact of the ingestion of specially processed cereals (SPC) optimized to enhance the synthesis of endogenus antisecretory factor (AF). The AF acts as a modulator of water and ion transport by regulating the homeostasis of chlorides. The intake of Omega-3 seems to satisfy all necessary requirements to obtain a correct homeostasis of the inner ear. Finally, the repetitive application of excess pressure in the middle ear (Meniett device), virtual reality and acupuncture have been shown to induce improvements in patients with Meniere's Disease.

### REDUCTION OF VERTIGO SYMPTOMATOLOGY WITH CHRONIC USE OF WEAK ASYMMETRIC BASE-IN PRISM SPECTACLES (WABIPS) IN **VESTIBULAR MIGRAINE PATIENTS**

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Reduction of vertigo symptomatology with chronic use of weak asymmetric base-in prism spectacles (WABIPS) in Vestibular Migraine patients.

### CERVICAL SPECIFIC PROTOCOL AND RESULTS FOR 300 MENIERE'S DISEASE PATIENTS FOLLOWED FOR A MINIMUM OF FIVE YEARS

M. T. Burcon Meniere's Research Institute

Testing efficacy of cervical specific care to control vertigo in 300 Meniere's patients. Pattern established utilizing Tytron thermography, Thompson cervical syndrome and modified Prill leg length inequality tests, determining when and where to adjust. Adjustment listings obtained by Blair x-ray analysis. There are four atlas listings under this system. Ninety percent of patients had atlas listings of posterior and inferior on the opposite side of the involved ear. When patients were in pattern, Palmer toggle recoil and/or Pierce Results knife-edge adjustments were performed. Vertigo intensity rated by 300 patients on a scale of 0 to 10, with 10 being the worst imaginable. Prior to treatment mean score was 8.5, six weeks post treatment average was down to 3.0, after one year 2.0, two years 1.4, three years 0.9, four and five years 0.8. an improvement of over 90%. Ninety seven percent claimed a dramatic improvement in vertico. Three percent had side effect of headache. Upper cervical subluxation complex resulting from whiplash can cause chronic Eustachian tube dysfunction from a combination of torquing CN V, which supplies the tensor veli palatine muscle, and swelling from facet friction imposing pressure on the auditory tube in the nasopharynx. This edema can over stimulate the sympathetic innervation of endolymphatic sac via the superior cervical ganglion, creating endolymphatic hydrops. The misalignment can traction CN VIII, disrupting hearing and balance, kinking the vertebral artery, which supplies blood to inner ear via the basilar artery. Since the cranial vault is a closed hydraulic system, lowered blood pressure will increase craniosacral fluid pressure via the cochlear aqueduct. Meniere's Disease can be caused by a structural problem resulting from whiplash. The correlation was not previously made because it takes an average of fifteen years from the time of the trauma to the onset of symptoms.

- Characterized by recurrent episodes of tinnitus, acute vertigo, sensorineural hearing loss and aural fullness, Meniere's Disease is
- debilitating impact on quality of life. Although the etiology and pathogenesis remain largely unclear, the most plausible hypothesis
- to endolymphatic hydrops abnormal fluctuations in the pressure of inner ear, which would be responsible for alterations in receptor
- The purpose of this paper was a review of the literature on complementary and alternative (CAM) methods currently available to
- The control of water intake may be the simpler and more convenient procedure for patients. Even the adaptation of the lifestyle and the



#### INTRATYMPANIC GENTAMINC/DEXAMETASONE VERSUS GENTAMICIN ALONE IN MENIERE'S DISEASE

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To evaluate the vertigo control rate and hearing outcome of intratympanic gentamicin/dexamethasone versus gentamicin alone in subjects suffering from unilateral definite Meniere's Disease.

103 patients met the 1995 American Academy of Otolaryngology-Head and Neck Surgery Committee on Hearing and Equilibrium Guidelines for the diagnosis of unilateral definite Meniere's Disease. All these subjects come to our tertiary referral center after unsuccessful treatment (no adequate vertigo control) with various medications (low dosage betahistine, diuretics, steroids). All subjects were treated for at least 6 months with high dosage betahistine (48mg twice/daily).

64 patients accepted to be treated either with gentamicin/dexamethasone mixture or gentamicin alone with the titration technique due to incomplete vertigo spells control or the will to stop oral medications. Patients were randomly assigned in the two groups. The mean follow-up was  $1.2\pm11$  years.

Substantial vertigo control (class A-B) was achieved in 93.1%, 94.7% and 71.2% respectively in the gentamicin/dexamethasone, gentamicin and betahistine groups.

Significant hearing deterioration (>15 dB HL) was observed in 6.4%, 10.2% and 5.7% respectively in the gentamicin/dexamethasone, gentamicin and betahistine groups.

No statistically significant differences were observed between the betahistine and gentamicin/dexamethasone groups (p>0.05). Gentamicin/dexamethasone inner ear perfusion may be the safest protocol treatment for vestibular ablation in disabling unilateral definite Meniere's Disease.

#### MANAGEMENT OF MENIERE'S DISEASE: OUR EXPERIENCE

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Meniere's Disease is characterized by spontaneous attacks of vertigo, fluctuating sensorineural hearing loss, aural fullness, and tinnitus. In the present study we analyze patient's characteristics, the clinical aspects, as well as the treatment strategy of Meniere's Disease. We also review the literature on the subject.

We conducted a retrospective study that included 215 patients diagnosed in our department with Meniére's disease. The diagnosis was made based upon the 1995 AAO-HNS criteria by the "Committee on Hearing and Equilibrium Guidelines for the Diagnosis and Evaluation of Therapy in Menière's Disease", as well as audiological and vestibular function tests results. Radiological evaluation included CT scan and MRI. Severity of vertigo, hearing level, and life style modification were evaluated after treatment in these patients.

In our series the majority of patients 182 /215 (84,6%) were controlled with medical treatment. Those who were refractory to medical therapy underwent surgery which consisted on: endolymphatic sac decompression in 24 patients, intratympanic injection of gentamicin in 7 patients, vestibular neurotomy in 2 patients. For these patients, the vertigo control rate was 75%, 57,1% and 100%, respectively.

Initial management of Meniere's Disease consists on medical therapy for the majority of patients, as well as life style modification. Surgical indications are rare, the choice of surgical procedure depends on the degree of serviceable hearing, severity of vertigo and condition of the contralateral ear. The results of surgery are generally satisfying.

### USAGE OF VASOACTIVE THERAPY IN CASES OF MODERATE TO SEVERE HEARING DISORDERS

D. Rancic, MD, PhD, Associat. Prof. Nis, Serbia

Usage of vasoactive therapy in cases of moderate to severe hearing disorders During the three year period(2013-2015), 51 patients of both gender (33 female and 18 male) with moderate to severe hearing disorders was followed up.

For therapy it was used in treatment: pentoxiphilinum, betahistinum, cinerizinum and polyvitamin therapy. Aim: To see efficiency of therapy

Length of treatment was from two to four months for each patient. Pure tone audiometry was performed before treatment and on every three weeks during admission of therapy. All data was processed by Kruskal-Wallis test.

Results: Better hearing in almost 90% patients with better hearing for high frequencies. (significance of p> 0.001)

### COMPARATIVE EVALUATION OF THE EFFECT OF THE MENIETT™ DEVICE IN PATIENTS WITH MENIERE'S DISEASE

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treatment and vestibular rehabilitation.

A randomized, placebo-controlled, double-blind, multicenter clinical trial of 6 weeks duration. Seventeen study sites all french speaking academic medical centers. Follow-up was performed by using diaries and questionnaires at each stage of the clinical study.

criteria was at least 2 vertigo episodes lasting more than 20 minutes and severed by 12 hours First step was a 8 weeks pre-selection phase that starts with placing a tympanostomy tube.

resolution of symptoms non inclusion to the second stage with device, ii) in case of active disease inclusion for a 6-week period, with active device or placebo device and iii) a 6-week period of run out after the treatment stop. Criteria was the evolution of vertigo episodes number lasting at least 20 minutes and with a free interval of 12 hours (20 mn-12 h) and their impact on daily life measured by self questionnaire.

So 97 patients were definitively included in this study, 49 using the Meniett device, and 48 the placebo one. The number of vertigo in 3 weeks decreased from 4.3 + 0.64 during the run in period, to 2.6 + 0.50 after 6 weeks of treatment, and to 1.8 + 0.82 after 6 weeks of the removal of the device, in the placebo group. Same results were observed in the Meniett group:  $3.2 \pm 0.46$  during the run in period, 2.5  $\pm$  after 6 weeks of Meniett treatment, and 1.5  $\pm$  0.29 after removal of the device. this study fails to demonstrate efficacy of Meniett device compared to placebo one. The decrease of the number of vertigo should be explained by an effect of the tympanostomy tube.



- Material and Method: 51 patient during three years period treated as outdoor patients with permanent control on each three weeks.

- To evaluate the efficacy of low pressure treatment with the Meniett device, in case of Menière's disease not controlled by medical
- Inclusion criteria: Adults presenting with Menière's disease characterized according to the AAO-HNS classification criteria. Inclusion
- Evaluation during 3 stages: i) Run in: during the 8 weeks pre-selection phase evaluation of tympanostomy tube effect: in case of
- 129 patients were enrolled in this study. 29 were not included because of the absence of vertigo after the tympanostomy tube insertion.



### INTRATYMPANIC GENTAMICIN FOR MENIERE'S DISEASE: SHORT- AND LONG-TERM FOLLOW-UP OF TWO REGIMENS OF TREATMENT

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The advent of intratympanic gentamicin (ITG) has reduced the number of more invasive procedures such as vestibular neurectomy. Although different treatment protocols of ITG injections are currently employed, over the years there has been a trend toward the use of lower amounts of gentamicin, in order to minimize the side effects, mainly represented by hearing loss and post-treatment imbalance.

The objectives of this study were the following: (1) to compare the results of two regimens of treatment with ITG at 2-year followup; (2) to evaluate the need and the efficacy of a retreatment after the recurrence of vertigo attacks in a longer period of follow-up (using the Kaplan-Meier method of analysis).

The study was designed as a retrospective chart review and carried on in a Tertiary referral center.

The study investigated 77 patients treated with intratympanic gentamicin (ITG). Thirty-five patients were treated with high-dose (HD) ITG (in total 6 injections, twice a day, repeated every three days) and 42 with low-dose (LD) ITG (1-2 injections). The results of treatment were evaluated in terms of functional level scale, control of vertigo, and hearing impairment.

At 2-year follow-up, a similar percentage of vertigo control was obtained in the 2 groups; the incidence of hearing loss and posttreatment disequilibrium was significantly higher in patients treated with HD-ITG. The long-term follow-up showed a control of vertigo attacks with a single round of treatment in 71.4% of patients treated with HD-ITG and in 55% of those treated with LD-ITG. With repeated rounds, an effective control of vertigo could be achieved in 88.5% using a HD-ITG protocol and 97.7% using a LD-ITG protocol.

LD-ITG allows obtaining good results in term of vertigo attacks associated with a limited occurrence of side effects. The long-term follow-up showed that LD-ITG needed repeated rounds more frequently than the HD-protocol. HD-ITG ran less risk of needing repeated rounds, but retreatment was ineffective in 40% of the cases requiring surgical therapy.

#### LONG-TERM RESULTS OF INTRATYMPANIC GENTAMICIN IN THE TREATMENT OF MENIERE DISEASE

I I Wazen MD Silverstein Institute, Ear Research Foundation

The purpose of this study is to determine the long-term success rate of intratympanic gentamicin in controlling the vertigo attacks in patients with disabling vertigo from Meniere Disease.

Patients treated with intratympanic gentamicin between May 2011 and May 2013 were followed, allowing a minimum of 2 years post treatment follow up, complying with the American Academy of Otolaryngology Head and Neck Surgery reporting guidelines. Patients were divided into 2 groups: those who received 40 mg/ml gentamicin by intratympanic injections, and those who were treated with the Microwick technique using 10mg/ml gentamicin daily. The length of the treatment in both groups was determined by repeated audiograms and videonystagmography including ice calorics on the treated side.

The incidence of recurrence of vertigo after successful control is reported with a description of subsequent necessary treatments: more gentamicin, destructive labyrinthectomy, or vestibular neurectomy.

The differences in response to treatment and hearing preservation between the two groups will be presented as well as the differences in the need for further treatments after vertigo recurrence.

Intratympanic Gentamicin is a highly effective minimally invasive in office method of controlling vertigo in Meniere Disease that has almost eliminated the need for the traditional hospital based procedures in our practice.

## SAC SURGERY

#### SAC SURGERY FOR TREATMENT OF MENIERE DISEASE

R Bento University of Sao Paulo - Brazil

In cases of persistent symptoms of vertigo in patients with Meniere's Disease, systematically used in endolymphatic sac surgery by the technique described by Paparella.

In this presentation we will show the technique and its results.

147 patients previously treated with various drugs and some with intratympanic injection of gentamicin and in which the symptom of vertigo remained underwent mastoidectomy with opening of the endolymphatic sac and placing a "Silastic" drain to the mastoid cavity. Consistent improvement or elimination of vertigo was observed in 94% of cases. In 32% of patients tinnitus improvement and 89% improvement of ear fullness.

#### OSTEOPLASTIC REFINEMENT IN ENDOLYMPHATIC SAC SURGERY

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The surgical approach to the endolymphatic sac requires a cortical mastoidectomy. In a normally developed mastoid air cell system removal of the mastoid cortex enbloc may be standard practice. This approach can be modified to maintain the preoperative postauricular contour by preserving the musculo-periosteal attachment to the cortex . The cortex and musculoperiostium can be elevated as an osteoplastic unit and "hinged" anteriorly along the lateral margin of the external canal. Upon completion of the mastoid dissection the cortex is restored to its anatomical position and the mastoidotomy closed. The application of the osteoplastic approach is not limited to sac surgery. It is especially well suited as an adjunct to the translabyrinthine removal of acoustic neuromas where the bone flap maintains compression on the fat graft and buttresses the repair. This demonstration is consistent with the osteoplastic principle applied elsewhere in the head and neck.



#### ENDOLYMPHATIC DUCT BLOCKAGE: A NEW ERA IN THE TREATMENT OF MENIERE DISEASE

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Endolymphatic sac surgery has been a favorable option for patients as it is a hearing preservation surgery and has a low surgical morbidity. The effectiveness of this surgery has been debated. In our Institution, we have, over the past few years, established a novel surgical technique for the treatment of Meniere's Disease: The Endolymphatic Duct Blockage(EDB). our aim is to compare the effectiveness of the EDB and the Endolymphatic sac decompression(ESD) to control Meniere's Disease symptoms and to evaluate their effect on hearing level.

we performed a prospective non-blinded randomized study in our tertiary medical center. 57 patients affected by a refractory Meniere's Disease were included out of which 22 underwent an ESD and 35 underwent an EDB. Five periods of follow-up were considered: 0 to 1 week, 1 week to 6 months, 6 to 12 months 12 to 18 months and 18 to 24 months. Mean outcome measurements consisted of vertigo control, tinnitus, aural fullness, instability and hearing level. Hearing level was evaluated using pure-tone average(PTA) and speech discrimination score(SDS)

There was no significant difference between the two groups in the number of vertigo spells per months preoperatively(p=0.153). Twenty four months postoperatively, 96.5% of the EDB group had achieved a complete control of vertigo spells against 37.5% of the ESD group with a statistically significant difference(p=0.002). There was a better control of tinnitus and aural fullness with EDB(p=0.021 and p=0.014 respectively). There was no statistically significant difference in hearing level preoperatively(p=0.976) and 24 months postoperatively(p=0.287) between the two groups. Hearing level was preserved in each group with no significant difference between the preoperative and the postoperative levels(p>0.05).

EDB is more effective than the traditional ESD in controlling the symptoms of Meniere's Disease. It is a novel surgical technique with promising results for a complete treatment of Meniere's Disease. There is no significant complications or adverse effect.

After these results, we stopped doing an ESD. We operated until february 2015, 113 patients with the EDB technique. The success rate continue to maintain the same percentage presented in the aforementioned data. In our presentation, we will show the participants a video of the technique et we will discuss the results, the difficulties, and the complications as well.

#### ENDOLYMPHATIC SAC REVISION SURGERY

M. M. Paparella Minneapolis, USA

Conservatism in Menieres's Disease precedes more radical or destructive therapy such as physical or chemical labyrinthectomy or vestibular neurectomy. ESR (8-10% of cases) as performed in hundreds of cases has not only been successful in ameliorating disabling symptoms of Menieres' disease usually for the patient's lifetime but it provides a powerful lesson in understanding the pathogenesis of Meniere's Disease. Findings include, fibrous and osseous invasion into the mastoid, Trautmann's triangle and extrinsic dura containing the endolymphatic sac rendering the dura very ridged. Alloplastic silicone t-struts and spacers are removed and are bright yellow unlike thousands of patients with tympanoplasty with the middle ear silastic implant spacer suggesting powerful osmotic and hydrostatic influences. After revision these patients have better results than those who have a primary surgical procedure. Here pathogenesis is visible in a living patient. Due to the natural history of the disease the patient develops incapacitating Menieres's disease. After endolymphatic sac enhancement the patient has a good result and often for many years. The pathogenesis is visible and consists of endolymphatic malabsorption and obstruction of the endolymphatic sac and dura.

## **CLINICAL ISSUES 4**

### DID PROSPER MENIÈRE DISCOVER MENIERE'S DISEASE?

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Prosper Menière had a lasting impact on otology in the whole world, since he built up a first international binding to foreign countries by translating the German textbook of Wilhelm Kramer into the French language from the English edition. Adam Politzer was the first foreign otologist to recognize the guiding significance of Menière's observation and was one of first next to Voltolini to use the term "Menière's disease". Up to now there is still doubt about what Menière himself originally described and the pathological condition which carries his name.

Since than, otologists in Germany and all over the world put their efforts in explaining the pathophysiology of this disease and in finding an adequate treatment. During decades, the academic discussion kept on and was not without controversies. Some even doubted the significance of Menière's disease as own entity.

The history about the scientific landmarks was not without tragedy. The first to depict the endolymphatic hydrops - Prof. Yamakawa became mostly unknown to the scientific world, because he did not publish in English, later suffered himself from Menière disease and his temporal bone bore evidence of hydrops as dissected post-mortem. Even the correct spelling of Menière's name became subject of discussion during years. A search in the French National Archive unambiguously depicted that Prosper Menière himself signed with only one accent grave on the second "e", which was undoubtedly testified by several handwritten letters of Prosper Menière.

### RE-EVALUATION OF QOL IN RELATION WITH SYMPTOMS OF MENIERE'S DISEASE

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Meniere's Disease (MD) is a chronic inner ear disease with attacks of disabling vertigo, progressive hearing loss, tinnitus and fullness. These symptoms, separately or in combination, cause great distress and have a considerable impact on the patients' quality of life. The purpose of this study is to determine the correlation between functional and audiological aspects of MD and psychological implication.

MD patients were submitted to the Dizziness Handicap Inventory (DHI) and the Zung Self-Rating Anxiety and Depression Scale. The test scores were correlated to age, sex, disease duration, unilateral/bilateral labyrinth involvement, duration/frequency of vertigo attacks, vestibular and auditory function, aural fullness, tinnitus, imbalance and functional disabilities.



### AUDIOLOGICAL CHARACTERISTICS. IMMUNOLOGICAL MARKERS AND CYTOKINES EXPRESSIONS IN COCHLEAR IMPLANT PATIENTS AFFECTED BY AUTOIMMUNE DISORDERS

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Aim: to investigate long-term audiological and electro-physiological outcomes, and serological characteristics of adult cochlear implantees (CI) affected by autoimmune/ dysimmune diseases, in comparison to matched group of non-autoimmune CI subjects.

30 Cochlear Implantees, with bilateral severe/profound SNHL, average age 58 (+8.7) years were assessed. 15 subjects were affected by autoimmune/dysimmune diseases (IC-AD): Relapsing Polychondritis (RP) (2), Cogan disease (3), autoimmune thyroiditis (2), aspecific systemic vasculitis (4), arthritis (3) and psoriasis (1). Control Group: 15 subjects, affected by otosclerosis (12) and chronic otitis (3) (IC-C). Immunological evaluation was carried out to identify: cytokines inflammatory serum markers (ICy) (IL-1β, IL-1RA, IL-10, PDGF, IL-2, IL-4, IL-8, IL-12, IL-17, INF-γ, MIP-1β, VEGF) (semiquantitative RT-PCR, Bio-Rad, Berkeley, California); serum autoantibodies (ANA, ANCA, LAC, ENA, Anticardiolipina) (Elisa test); anti HSP-70 autoantibodies (Otoblot assay, Immco). Audiological evaluation was carried out under Free Field conditions both in Quiet and in Noise (primary signal presented at 65dB, 0 azimut; Noise competition presented at Speech Noise Ratios, SNR, +10 and +5dB, 0 azimut). Electric Impedance values (kOhm)and M-Levels (CU) were obtained in all patients and analyzed by means of non-parametric statistics. A low positivity for serum autoantibodies and HSP-70 was found in all CI subjects, not significantly different between IC-AD and IC-C. Pro-inflammatory cytokines IL-1β, INF-y and VEGF were significantly higher in IC-AD subjects. Both groups performed very well for speech perception in guiet for both word (mean= 88% versus 90% for IC-AD and IC-C respectively) and sentence recognition tests (mean= 88% versus 85% for IC-AD and IC-C respectively). Both groups performance deteriorated when listening in the presence of noise especially with the more adverse SNR. Statistical analysis did not show any significant differences between the two groups (p>0.05). Impedances showed higher and more unstable values in IC-AD patients.

AD-CI patients showed good long-term audiological results, comparable with CI-C subjects. Serological autoimmune Ab and HSP-70 confirmed low sensitivity and specificity (Matsuoka, 2013) while higher I-Cy might underlies a chronic inflammatory process (Pathak, 2011) which could be still active in some of the CI-AD patients. Chronic inflammation might be responsible for intra-cochlear fibrosis, higher and more unstable electrical impedances and more frequent programs' adjustments.

#### ENDOLYMPHATIC SAC REVISION SURGERY

M. M. Paparella Minneapolis, USA

Acute vertigo with spontaneous nystagmus(acute vestibular syndrome, AVS) is generally of peripheral origin. But recently, it was proven that when a patient with AVS has a negative catch up saccade on the head impulse test(HIT), a central lesion is strongly indicated. However, some AVS patients finally diagnosed as peripheral vertigo can show a negative HIT. The purpose of our study was to analyze the clinical manifestations of this group of patients.

From March 2013 to July 2014, 155 patients with AVS underwent the video head impulse test(vHIT) in Kangbuk Samsung Hospital. Of these 155, 31(20%) had a negative lateral canal vHIT, and a retrospective analysis was done on the records of the 31 patients. Data on the diagnosis, results of videonystagmography(VNG), gain of lateral canal vHIT, caloric test and cervical vestibular evoked myogenic potential(cVEMP) were analyzed. Of the 31 patients, the most common diagnosis was Meniere's Disease, with 17(54.5%) cases. The next most common diagnosis was sudden sensorineural hearing loss with 6(19.3%) patients, and a central lesion was the third most prevalent diagnosis, with 3(9.7%) cases. Of the 17 patients with Meniere's Disease, 9(52.9%) had a spontaneous nystagmus beating toward the ipsilesional side, and the remaining 8(47.1%) patients had a contralesional beating nystagmus. 5(29.4%) of the 17 patients with Meniere's Disease had caloric paresis. The average Jonkee's index of the 5 patients was 37.4, and their average gain on lateral canal vHIT was 1.05. Of the 6 patients diagnosed with sudden sensorineural hearing loss, none had canal paresis, but 5(83.3%) patients had asymmetry on cVEMP. All 3 patients diagnosed with central vertigo had vascular lesions associated with the cerebellum. Analysis of the spontaneous nystagmus on VNG of the 31 patients revealed that 29(93.5%) patients had a maximal slow phase velocity of 5 degrees or lower.

Clinically, a negative HIT has importance to diagnose stroke in patients of AVS. But, a significant number of cases with negative HIT were finally diagnosed as peripheral origin. Therefore, a negative HIT may not always indicate a central lesion, especially in acute isolated vertigo patients.

#### POSSIBLE ROLE OF HERPESVIRIDAE FAMILY VIRUSES IN THE PATHOGENESIS AND EVOLUTION OF SENSORINEURAL HEARING LOSS

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The viral etiology has been the best studied hypothesis for idiopathic sensorineural hearing loss and has been so far supported indirectly by medical, clinical and serological history. The discovery of the virus within the inner ear can add information about the possible etiology and allow to investigate the pathophysiological basis of hearing loss. The purpose of this study was to identify the genome of Herpesviridae family viruses in the endolymphatic fluid of hearing impaired patients undergoing cochlear implant surgery. 31 patients, aged between 1 and 69 years, suffering from sensorineural hearing loss, were subjected, during the cochlear implant placement, to a withdrawal of inner ear fluid. In each sample we looked for several viruses (HSV-1, HSV-2, CMV, VZV, EBV, Enteroviruses, Adenoviruses) through the use of two molecular methods and specific primer sets. Radiological exams, serology (specific IgG and IgM antibodies) and PCR of peripheral blood were also performed on the patients. While the search of the viral genome in peripheral blood was negative in all patients, in 3 patients it was found in the cochlea: 2 patients were positive for CMV and 1 for HSV-1 DNA. The detection of the viral genome of CMV and HSV-1 in the endolabyrinthine fluid, collected from patients with hearing loss, in the absence of acute viral infection or congenital one, seems to show the ability of these viruses to remain in latent phase in the spiral ganglion and cause a persistent infection. This study supports the hypothesis that Herpesvirus (HSV-1 and CMV) may have a reactivation of a past and latent infection, suggesting a possible etiological role of virus (when acquired in post-natal age) in the genesis of idiopathic hearing loss.

#### SUPER PARAMAGNETIC NANOPARTICLES DRIVEN BY EXTERNAL MAGNETIC FIELD FOR TARGETED DRUG ADMINISTRATION TO INNER EAR: FEASIBILITY AND TOXICITY

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Superparamagnetic nanoparticle (SPMN) can vehicle in an active and targeted manner several types of therapeutic molecules including steroids and peptides. Theoretically, they can access the cochlear apex from the round window without generating hydrostatic pressure and avoid blood perilymph barrier. The aim of this study was to develop an in situ drug administration method with these particles to study their mobility and toxicity.

Five adult Wistar rats were included. The left tympanic bulla was opened under general anesthesia. The round window membrane was perforated with a micro-needle and 5 µl of SPMN (iron oxide) at 5 mg/ml suspended in hyaluronic acid gel (Healon<sup>®</sup>) was applied on the membrane. A muscle fragment was placed on the membrane to seal the perforation. The wound was closed. The right ear served as control. SPMN were mobilized by a rare-earth magnet (542 mT) in 4 different positions around the head for 10 min each in order to attract SPMN toward the apex. Hearing was monitored at 2, 8,16 and 32 kHz with ABR and tone bursts before and immediately after surgery, 7 days and one months after administration. Histological study of the cochleae was conducted 1 month after surgery. The procedure took 56 minutes in average. Hearing was completely preserved in all cases. Thresholds at 2 and 8 kHz remained unchanged. Immediately after surgery, thresholds increased at 16 kHz ( $46 \pm 18,2$  dB SPL versus  $32 \pm 4.5$  dB for control) and 32 kHz  $(58 \pm 17.9 \text{ dB SPL versus } 46 \pm 5.5 \text{ dB for control}, p < 0.01$ , Friedman test), but returned to normal at 7 days. Microscopic examination showed SPMN in the basal turn in 3 cases and in the second turn in 2 animals. SPMN could also be observed in stria vascularis in one case.

We showed that SPMN can be driven inside cochlea without affecting the hearing up to one month after administration. Penetration in the stria vascularis suggests a possible route of elimination of these particles.



#### A STUDY FOR LOCAL TREATMENT OF THREE DIFFERENT POLYMERS AIMED FOR MIDDLE EAR ADMINISTRATION

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Recent advances in inner ear research support the idea of using the middle ear cavity for drug administration to target the inner ear. Rheological and safety assessments of three candidate polymer formulations for intra-tympanic drug administration is tested. The formulations were based on sodium carboxymethyl cellulose (NaCMC), sodium hyaluronate (NaHYA), and poloxamer 407 (POL). Rheological studies were performed with a controlled rate instrument of the couette type. Safety studies were performed in guinea pigs subjected to an intra-tympanic injection of the formulations. Hearing function was explored with ABR before and 1, 2, and 3 weeks after the injection. Elimination of the formulations marked with coal was explored with an endoscopic digital camera 1, 2, and 3 weeks after injection. Middle and inner ear morphology was examined with light microscopy 6 days after injection.

NaHYA did not cause prolonged hearing threshold elevations. The results of the elimination and morphological investigations support the conclusion of NaHYA being most promising.

A formulation based on sodium hyaluronate (NaHYA) was the best candidate vehicle for intra-tympanic drug administration regarding conductive hearing loss, inflammatory reactions, and elimination.

## **VESTIBULAR FUNCTION AFTER CI SURGERY**

#### COMPARISON OF THE RESULT OF CALORIC TEST VS VIDEO HEAD IMPULSE TEST IN COCHLEAR IMPLANT USERS

#### S. A. Incesulu

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Cochlear implantation (CI) is widely accepted procedure for the patients with bilateral severe to profound hearing loss. In general, it is a safe method with low complication rate. One of the complication is vestibular disturbance and it has been reported between 31-75 % in the literature. Incidence of balance problem is also higher in hearing impaired patient. Vestibular disturbance after CI may due to changes in fluid homestasis of the inner ear, inflammation due to surgical trauma or loss of hair cells

Evaluation of vestibular system may require several different kinds of tests besides detailed history and physical examination including oculomotor and vestibulooculer reflex evaluation, positioning tests, evaluation of cerebellar function. Laboratory tests consists of videonistagmography including caloric test, evoked vestibular myogenic potentials, rotational chair, computerized dynamic posturography and recently video head impulse test (vHIT)

Caloric test and vHIT evaluate the vestibuloocular reflex. Caloric test is a test of the lateral semicircular, it does not evaluate vertical canals or otolith function. It gives information about the symmetric or asymmetric function of the canal. Low frequency stimulation is used in caloric test. vHIT is a test of three semisircular canals and high frequency stimulation is used.

In this study, twenty patients who underwent unilateral cochlear implant in Otolaryngology Head&Neck Surgery Department, Eskisehir Osmangazi University Faculty of Medicine were evaluated. Lateral semicircular canal functions were assessed by using caloric and video head impulse tests. Moreover, vertical canal function which was obtained from the vHIT was also noted. Three patients were reimplanted because of the device failure. Results were compared with etiology, duration of cochlear implant use and subjective vertiginous symptoms which was evaluated by dizziness handicap inventory.

# VESTIBULAR FUNCTION BEFORE AND AFTER COCHLEAR IMPLANTATION IN PATIENTS WITH POSTLINGUAL DEAFNESS: A PROSPECTIVE OBSERVATIONAL STUDY

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Assess vestibular function before and after cochlear implantation (Cl) in adult patients with postlingual deafness. Vestibular assessments: questionnaire assessing vertigo, caloric tests (CTs), rotary chair testing, and computerized dynamic posturography (CDP), were sequentially performed for 24 patients before and 60, 120, 180, and 365 days after Cl. Dizziness remained unchanged in 7.7%, improved in 84.6%, and worsened in 7.7% of the cases. Baseline CTs identified 29.2% patients with normal reflexes, 33.3% with unilateral areflexia or hyporeflexia, 12.5% with bilateral hyporeflexia, and 25% with bilateral vestibular loss (BVL). Most patients exhibited objective improvements in postural stability, as evidenced by the CDP. Balance improved at 365 days after Cl in all patients. Patients with BVL used visual information for postural stabilization. Preoperative vestibular assessment findings should be documented because postural recovery over time depends on this information.

#### VESTIBULAR FUNCTION AFTER COCHLEAR IMPLANTATION IN PARTIAL DEAFNESS TREATMENT

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Cochlear implantation is worldwide fully accepted method dedicated to patients with total or partial bilateral deafness. Nevertheless, vestibular and balance disorders are still one of the common complaints among the patients after the operation and while using the implant. According to the literature data, the percentage of vestibular symptoms ranges from 5,9% to 80% and that of vestibular examination abnormalities from 20-60%. Hearing preserving methods, that are proven to be successful in protecting cochlear function, are supposed to diminish vestibular disorders after operation. The aim of the study is to assess vestibular status and vestibular symptoms after cochlear implantation in patients with partial deafness, using hearing preserving methods, emphasizing on the sacculus and utricle function.

All the patients (43patients; 24male, 19female, middle age 41y.o.) included in the study were divided into three groups according to the type of implantation that was applied. These groups were as followed: PDT-EC (Partial Deafness Treatment - electrical complement), PDT-EAS (Partial Deafness Treatment – electric-acoustic stimulation), PDT-ES (Partial Deafness Treatment – electric stimulation). In each case, the implant was inserted by round window approach (RWA). The patients underwent cVEMP and oVEMP examination before, 1-3months and 6-9months after the operation. The assessment was completed by fulfilling the questionnaire describing vestibular symptoms. In VEMP responses the latencies, corrected amplitude and ratio of post- to preoperative amplitude were measured.

After introducing RWA (round window approach) and soft electrode insertion the rate of vestibular complications has significantly decreased. Vestibular symptoms were rare, mostly transient and in early postoperative period. Only one patient in our study group, with coexisting EVAS, lost VEMP response postoperatively. However, in every single case the corrected amplitude measured postoperatively was decreased. There was no correlation between changes in VEMP response and the frequency of vestibular symptoms. Hearing preserving methods (round window approach, soft electrode insertion) are protecting for vestibular organ.



7<sup>th</sup> International Meniere's Disease Inner Ear Disorders



## **KEYNOTE LECTURE 7**

#### PERSONALIZED MEDICINE FOR COCHLEAR IMPLANTS

**Zenner HP** Friese N Dept. of Otolaryngology, The University of Tübingen

Personalized medicine using molecular genetics of functional proteins like Otoferlin, Connexin 26, KCNQ4, or of Usher gens play a growing role for the indication of cochlear implants.

It serves for the stratification of patients. This is thought to widen specific indications predominantly for pediatric cochlear.

## **EFFECT OF CI ON MENIERE DISEASE**

#### STRATEGY FOR END-STAGE MENIERE'S DISEASE: LABYRINTHECTOMY WITH CI

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Objective: Compare the pre and postoperative performance in patients undergoing cochlear implantation (CI) for recalcitrant Meniere's Disease.

Study design: Prospective

Setting: Tertiary center, University of Iowa Cochlear Implant Center

Patients: Forty-six patients have undergone CI for single sided deafness (SSD) at our institution. SSD was due to end-stage Meniere's Disease (MD) in 18 subjects. In these patients the CI was placed simultaneous with a labyrinthectomy.

Intervention(s): CI with labyrinthectomy.

Main outcome measure(s): Speech perception and localization data was collected pre- and post-operatively at 3, 6, 12, and annually. CNC word and AzBio sentences in quiet tests were administered post-operatively via DirectConnect to the sound processor. Multipleloudspeaker sound localization and adaptive HINT speech perception in noise tests were collected in the bilateral and better earonly listening conditions. Additionally, the Tinnitus Primary Function Questionnaire was administered pre- and at 12 months postoperatively.

CNC word and AZ Bio sentence scores significantly improved in the implanted ear. Sound localization was better for most subjects in the bilateral condition verses when tested in the better ear-only condition. Binaural benefits in noise were demonstrated through significant head shadow and binaural summation effects. Most patients reported diminished tinnitus in the subcategories of Emotions, Hearing, Sleep and Concentration. All patients undergoing labyrinthectomy experienced resolution of vertigo attacks and were satisfied with the Cl.

A CI restores binaural auditory function individuals with a unilaterally deafened ear. Additionally, the binaural input appears to improve sound localization and speech perception in noise for most patients with normal hearing in the contralateral ear. Most patients experience a reduction in their tinnitus handicap after receiving a Cl. These functions cannot be restored using bone conduction hearing devices or cross hearing aids. In patients with severe hearing loss and recalcitrant vertigo attacks due to MD, simultaneous labyrinthectomy and CI effectively relieves vertigo attacks and improves auditory function.

#### TRANSLABYRINTHINE VESTIBULAR NERVE SECTION AND SIMULTANEOUS COCHLEAR IMPLANTATION IN PATIENTS WITH RECALCITRANT MENIÈRE'S DISEASE: PRELIMINARY REPORT

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Surgical management of Menière's disease (MD) is recommended in case of medical and intratympanic treatment failures. Surgical options aim to control vestibular symptoms and improve cochlear impairment. George Portmann introduced the concept of conservative surgery with the endolymphatic sac approach. However, its effects are quite controversial and many Authors have questioned which technique leads to the best results. Only well selected cases with intractable unilateral definite MD may be properly addressed to ablative surgery, where its effectiveness on vestibular symptoms is assessed by international literature. Destructive procedures on the inner ear are reserved to patients with unusable hearing and in particular, translabyrinthine vestibular nerve section (TLVNS) seems to lead to the best control for vestibular symptoms. Cochlear implantation (CI) has been proved to be safe and effective in patients with MD also after destructive procedures on the inner ear. In 1975, Brackmann first published the results of Cl after TLVNS: since then no more experiences have been reported. We carried out a bi-centric prospective study to evaluate the effectiveness of TLVNS and simultaneous Cl in patients with recalcitrant MD. Our preliminary results were analyzed and discussed. The study was carried out at the Department of Otorhinolaryngology, University of Pavia, Foundation IRCCS Policlinico S. Matteo and at the Otorhinolaryngology Unit, Ospedale Civile "SS Antonio Biagio and C. Arrigo", Alessandria, (Italy). All adult patients (over 18 years of age) with a diagnosis of intractable unilateral definite MD and unusable hearing were enrolled after medical and intratympanic treatment failures. Pre- and postoperative otoneurological evaluation concerned: pure-tone and speech audiometry, tinnitus handicap inventory test, frequency of vertigo attacks, functional level scale and rate of vertigo control according to the 1995 AAOHNS guidelines, dizziness handicap inventory test, MD patient-oriented severity index, head impulse test and caloric testing. Six patients met the specific inclusion criteria, but only 5 subjects were submitted to TLVNS with simultaneous CI: one case refused the ablative procedure and was addressed to the endolymphatic sac surgery. One patient was lost to follow-up due to geographic reasons. Despite the few numbers of the examined population, in all cases we recorded a clear improvement of vestibular and cochlear symptoms. In particular, we observed a complete control of vertigo (class A according to the 1995 AAOHNS guidelines) with beneficial results of quality of life. Hearing improvement was overall reported, but the level of subjective satisfaction was linked to the degree of hearing impairment of the non-operated ear. Follow-up ranged from 1 to 40 months. In conclusion, TVLNS with simultaneous CI shows promising findings, even though a greater number of patients with a homogeneous long-term follow-up are needed to fully evaluate the real benefits of this procedure.

#### REHABILITATION OF FLUCTUATING HEARING LOSS BY COCHLEAR IMPLANT

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#### This retrospective study evaluated the performances of the cochlear implantation (CI) in adults with fluctuating hearing loss, due to autoimmune disease or Menière's disease.

Thirteen patients (age: 22 to 73), with uni- (n=6) or bilateral (n=8) severe to profound fluctuating hearing loss, underwent a Cl on one (n=12) or two ears (n=1). In cases of unilateral severe/profound hearing loss, the fluctuating hearing loss on the contralateral side induced very high difficulties to fit the hearing aid (HA). Menière's disease was evidenced in 8 cases, Cogan's syndrome in 1 case, and autoimmune disease in 2 cases. The aetiology was unknown in 3 cases. Performances were tested in free field, without lipreading, with disyllabic words recognition in quiet, and sentences in quiet or noise (SNR 10 dB). The mean follow up was 19 months after the implantation. Compared to preoperative data, CI clearly improved the performances in the patients with bilateral profound hearing loss in quiet (disyllabic words: 80% versus 67%; sentences: 94% versus 70%), and especially in noise (75% versus 27 %). For patients who still had benefit of their contralateral hearing aid, the performances were also increased (disyllabic words: 98% versus 87%; sentences: 98% versus 91%; sentences in noise: 75% versus 48%). It should be noticed that their hearing aid clearly brought gualitative benefit on daily communication. In uni- or bilateral fluctuating hearing loss, Cl is a good opportunity to restore high level of communication on quiet and noisy situations. Due to difficulties to treat these patients by medical treatment (steroids, immuno suppressor...), and to fit HA, Cl should be discussed as early as possible. Learning outcomes: Strategy of hearing rehabilitation in patients with uni or bilateral fluctuating hearing loss.



#### COCHLEAR IMPLANTATION AS THERAPY OPTION IN SINGLE-SIDED DEAFNESS AND VERTIGO CAUSED BY M. MENIERE

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M. Menière leads to a deafness on the affected side in many cases. The intensity of the vertigo usually decreases over time, after initially being guite strong, however, the vertigo is persisting in most patients. The vertigo combined with the deafness result in severe suffering. The cochlear implant has been established as a very successful therapy option for single-sided patients, so the extension of the indication for patients with M. Menière has to be evaluated.

5 patients (2 SSD, 3 AHL) were examined in a retrospective analysis, having been provided with a cochlear implant between 2009 and 2014 with deafness in M. Menière. Extensive audiological tests were done during CI preop evaluation and after 6 and 12 months after surgery. Subjective evaluation was done with the SSQ questionnaire.

All 5 patients had a successful surgery. The results of the tests were comparable to those of other SSD and AHL patients with other underlying diseases. 2 out of 5 patients suffered from vertigo after surgery; this could be treated with Cortison infusions successfully. The results confirm the binaural hearing gain with the CI. Cochlear implantation should be evaluated as a therapy option when there is no sufficient benefit by conventional hearing aids in patients with deafness due to M. Menière in combination with severe hearing loss and frequent vertigo.

#### SPATIAL HEARING IMPROVEMENT AND LONG-TERM SUPPRESSIVE EFFECT ON TINNITUS AFTER COCHLEAR IMPLANTATION IN SINGLE-SIDED-DEAF PATIENTS WITH AND WITHOUT MENIERE'S DISEASE

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Cochlear implantation (CI) has the potential to significantly reduce tinnitus in single-sided-deaf (SSD) patients and to restore binaural hearing. The current study presents the long-term evaluation of the auditory and tinnitus outcomes up to 10 years with specific interest to Meniere's Disease (MD).

Long-term evaluation was derived from 4 MD and 19 non-MD patients suffering from SSD and accompanying incapacitating tinnitus. The latter was defined as tinnitus loudness visual analogue scale (VAS) score exceeding 6/10. Patients had normal hearing or mild to moderate hearing loss on the contralateral ear. They were received the Cl at a median age of 55 years (ranging 22 - 71 years) and had 8 years (ranging 3 - 10 years) of experience with their Cl.

All patients wore their Cl seven days a week. It appeared that in all but one, Cl switch-on is the first act when rising and Cl switchoff is the last act before bedtime. In the majority of the patients (i.e. 70%) the tinnitus reduction started within one minute and the residual inhibition after CI switch-off was less than a minute (in 65% of the cases). The long-term tinnitus VAS scores indicate a significant improvement between the CIOFF condition (7.95/10) and the CION condition (2.85/10). The TQ also showed a significant tinnitus relief that remained stable over 8 years. Speech perception in noise and sound localization improved significantly after cochlear implantation. No statistically significant differences were observed between MD patients and the other patients.

Cl can significantly improve speech perception in noise and restore binaural hearing in SSD patients. Several years of Cl use are necessary to fully take advantage of binaural cues available from the CI. The accompanied tinnitus relief appears to be stable over 10 years of follow-up, even in MD patients.

#### OUTCOMES OF COCHLEAR IMPLANTATION IN END STAGE MENIERE'S DISEASE: A MULTICENTER STUDY

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The beneficial effect of Cochlear implantation (CI) in Meniere's Disease (MD) patients has been reported only in few works addressing small groups of heterogeneous patients.

We performed a retrospective study on the series of MD patients admitted to three tertiary care academic medical centers in Italy, from 2005 through 2013. The aim of this study was to evaluate the effectiveness and post-operative outcomes of Cl in MD and to relate them with the duration and the stage of the disease, with the degree of pre-operative residual hearing and speech discrimination scores, with the contralateral hearing level and with the patients' age. Twenty-one Cls were performed in 20 patients with bilateral definite MD. Age, symptoms at admission and previous ablative procedures were recorded. Pure tone and speech audiometry, vestibular testing and QOL guestionnaires were obtained. Main outcome measures: postoperative speech perception (word recognition scores -WRS -), cure rate for vertigo attacks (AAOO 1995) and subjective satisfaction (VAS) scores. The hearing and vestibular results were contrasted with the duration of disease, preoperative hearing level and patients' age.

Mean long-term follow-up was 37 months (24-78). The mean age at implantation was 57 years. At the time of Cl, 5 out of 20 patients presented active MD. Twelve patients had previously undergone unilateral chemical ablation of the labyrinth and were implanted on the same side; one patient simultaneously underwent a trans-labyrinthine removal of a vestibular schwannoma with sparing of the cochlear nerve and a Cl. Another received a sequential bilateral implant, Different brands and implants models were used; the limited numbers did not allow an adequate statistical analysis on this variable. Postoperative speech perception significantly improved in all cases (average WRS in guiet= 85%, p< 0.05). Fluctuations in Cl performance were observed in 6 MD patients.

The perceived hearing handicap showed a significant improvement after CI. (62%, p < 0.05). Among the 5 patients with recurrent vertigo before Cl, 4 had complete remission and 1 had substantial improvement. All others did not complain of vestibular disturbance after the Cl.

Speech perception outcomes in Meniere's CI recipients do not differ from those in adults with other acquired hearing losses . Cl in the end-stage of MD is a valid treatment option. As a collateral benefit, it can prove curative for vertigo spells, if the ear with the active MD is implanted.





#### COCHLEAR IMPLANT IN ASYMMETRIC MENIERIC HEARING LOSS

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Background: Bilateral severe to profound hearing loss is a standard criterion for cochlear implantation (CI). Patients with severe to profound hearing loss in one ear and a more moderate hearing loss in the other ear (i.e. asymmetric hearing) are not typically considered candidates for cochlear implantation. A significant number of subjects suffering from Menière's disease (MD) has severeto-profound hearing loss in the affected ear. When this occurs bilaterally or when a patient has a more moderate hearing loss in the contralateral ear, in which the amplification are often unsuccessful because of limited benefit, these patients may meet criteria for cochlear implantation.

Object: the purpose of this study was to analyse the post-operative results in patients suffering from Meniere disease and asymmetric hearing loss.

#### Study design: observational retrospective chart.

Materials and methods: fifteen subjects (10 males and 5 females) with either bilateral MD or unilateral MD who underwent CI in their ear affected with MD. The mean age at CI was 58,8 years (SD 11,5, range: 41-74). Nine subjects were implanted with a Nucleus multichannel device (Cochlear LTD, Sydney, Australia), three patients with an Advanced Bionics multichannel device (Advanced Bionics AG, Stäfa, Switzerland) and the remaining three with a Med-El device (Med- El Gmbh, Innsbruck, Austria). Nine subjects wore a CI on one ear and a hearing aid on the opposite side ("bimodal stimulation"). The remaining six recipients wore a unilateral CI. The PTA (500-4000 Hz) was 121,6 dB HL (SD+/- 0.8) on the CI ear and 78.4 dB HL (SD+/- 3.9) on the contralateral ear. At time of study, the Cl experience at testing was 31.4 months (SD +/- 29.4), ranging from 1 to 84 months. The audiometric measures included disyllabic word lists in noise at +5 dB SNR. The Speech, Spatial and Qualities of hearing scale (SSQ) was assessed pre and post-operatively such as the Tinnitus Handicap Inventory (THI).

Results: All patients use the device all the day with a mean of 13 hours. No intra-operative complications occurred. Only one subjects presented vertigo in the post-operative period with a resolution after 3 weeks. After Cl, the hearing of all subjects improved significantly as did their speech recognition in noise. Speech recognition in noise showed a mean improvement of 45%. The results were less clear for the treatment of vertigo associated with Menière's, as some patients continued to have vertigo spells after implantation. Tinnitus scale (THI) showed a positive effect of CI stimulation and the SSQ results revealed an overall benefit of CI use. Some patients experienced alterations in their implant performance in association with fluctuations in vestibular symptoms. Conclusion: This study demonstrates that Cl is an adequate treatment of speech perception for subjects with Menière's disease who

go on to develop asymmetric hearing loss.

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## **AUDIOLOGICAL TESTING**

AUDIOLOGICAL SCREENING IN CHILDREN WITH CEREBRAL PALSY

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The problem of cerebral paralysis remains one of the most pressing problems in modern medicine. Its importance is determined by the increasing prevalence of the disease and the social significance and occupies one of the avant-garde position of disabling diseases of children and adolescents. Currently, there is a steady increase in the number of patients with cerebral palsy. The frequency of cerebral palsy in foreign countries is about 2-3 per 1,000 newborns in Uzbekistan - 8.9 cases per 1,000 newborns. The most significant in the clinical picture of cerebral palsy is not only the defeat of the propulsion system and the intellectual and psychic sphere, but also a violation of the auditory analyzer, which in turn affects the secondary language delay and mental development. According to foreign data in children with cerebral paralysis of speech is 65-85%, and hearing loss is seen in 10-15% [Freeman M,2006].

The aim of this study is - to study the state of the auditory analyzer in children with various forms of cerebral palsy by screening. Materials and methods. The material of this study includes 67 (134 ears) children with various forms of cerebral palsy (Table №1, №2), were hospitalized in a specialized Neurological hospital, in Tashkent. Screening group consisted of children from 6 to 16 years old, boys- 36 (53.7%) and girls with 31 (46.3%). The largest number of 47 (71%) children were with common forms of cerebral palsy (spastic diplegia, hemiparetic, atonic-astatic form). With the most severe (hyperkinetic and double hemiplegia) were - 20 (29%) children.

Results. The study of auditory function was examined on the device "Neuro-Audio-Screen" Company Neurosoft (Russia) TEOAE two classes: transient evoked otoacoustic emission (TEOAE) and emission at the frequency distortion product (DPOAE). All studies were conducted in soundproof chamber in the waking state. To exclude results pseudo-deafness, all children held otorhinolaryngological examination to detect inflammation in the nasal cavity, oropharynx, external and middle ear, estimated the number of cerumen in the ear canal, and at the same time define the personality of the size of the insert for each child.

Conducting DPOAE revealed the following results: 67 of the child test is passed in both ears in 39 children (78 ears), in one ear - in 18 children (36 ears), the test failed on both ears in 10 children (20 ears). Conducted simultaneously study of auditory function by TEOAE gave somewhat different results: 67 of the child test is passed in both ears in 48 children (96 ears), in one ear - in 5 children (10 ears), the test fails on both ears in 14 children (28 ears).

The high prevalence of latent occurring diseases of the middle and inner ear in early childhood in patients with cerebral palsy, accompanied by hearing loss, causes the need for mandatory audiological examinations. Investigation hearing at an early age with the help of screening methods contributes to the timely detection of hearing impairment.

### CHARACTERISTICS OF HEARING ANALYZER MASKER IMMUNITY WHILE MENIERE'S DISEASE

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#### Introduction

Hearing status of so called healthy ear has a distinctive importance in specifying pathogenesis of early and particularly for differential diagnosis of unilateral Meiner's hearing loss, for investigation of which method of speech audometry is used against the background of noise (masker)

Absolute silence in human life is extremely a rare thing. In daily life, man perceives the speech signals not in isolation, but in different acoustic environments in which a big stress falls on hearing system identification and isolation of the desired information signal, which depends on the noise immunity acoustic analyzer. Methods

21 patients aged 26-58 years with typical complaints and with the diagnosis of unilateral hearing loss were examined. Noise-immunity of the acoustic analyzer was determined by speech audiometry in the free sound field conditions without interference, at the background of white noise and extraneous speech, separately for the ill and the healthy ear. Results

The definitions of speech discrimination of ill ear on the background of noise and speech Masker are consistent with those existing in the literature. During the study of the healthy ear, although up to 100% intelligibility, a phenomenon of phonemic regression was observes up to 93.6 + -2.2%, on the contrast with the control group, even without any interference. At the background of the noise 60dB intelligibility remained the same as in the silence. The degree of phonemic regression on the background of speech masker was expressed in somewhat higher extent than on the background of noise-respectively 87 + -2.8% and 93.5 + -2.5%. Conclusions

Thus, as a result of our investigations the intelligibility deteriorated with the phenomenon of phonemic regression or phonemic violation of noise immunity on the background of noise and speech Masker among the patients with Meniere's Disease of both the patient and the healthy ear with the prevalence of the masking effect of the speech Masker was revealed. Taking into consideration the absence of hearing loss according to routine (tonal) audiometry of the healthy ear, the data ireceived indicate bilateral disease and can be used for differential diagnosis of unilateral hearing loss.

#### ECOG FINDINGS IN PATIENTS WITH MENIERE'S DISEASE

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Meniere's Disease (MD) is an inner ear disorder characterized by sudden episodes of vertigo associated with tinnitus and pressure in the affected ear. Fluctuating hearing loss in the earlier stages typically leads to a permanent hearing deficit with a moderate-to-severe disability. The aim of this study was to analyze the electrocochleography (EcoG) findings and their correlation with other audiological tests in patients with definite MD. ENT examination, clinical history, pure tone audiometry (PTA), speech audiometry and extratympanic ECoG evaluations were performed in 33 patients with unilateral definite MD. Thirteen patients were male, 20 were female and the mean age was 45.9 + 13.5 years. The relationship between the summating potential to action potential (SP/AP) ratios and other audiometric parameters were evaluated. Mean PTA air conduction hearing thresholds were 48.2  $\pm$  24.8 dB HL at the pathological ears, and 19.1  $\pm$  13.9 dB HL at the healthy ears of the patients. 64.8% of patients had abnormally elevated SP/AP ratios. Correlation coefficients between SP/AP ratios and mean PTA thresholds were significant (p<0.05). EcoG is a valuable part of the diagnostic tool in the diagnosis of hydrops, as it is a non-invasive, easy to handle procedure.



7<sup>th</sup> International Meniere's Disease **Inner Ear Disorders** 



#### AUDIOMETRIC CONFIGURATION FOLLOWING EXCESSIVE NOISE EXPOSURE

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Aim:To determine the configuration of pathologic audiograms in patients with excessive noise exposure, and to calculate the frequency of audiometric notch in patients with and without excessive noise exposure by avoiding the effect of age-related hearing loss.

Methods: We analyzed 514 audiograms of 257 patients aged 20 to 50 years. A total of 240 patients (mean age of 38.7 years) had positive noise history and 17 patients (mean age of 41.2 years) with audiometric notch, but without history of excessive noise exposure. All patients were civilian examined at the Department of Otorhinolaryngology, City General Hospital "8-September", Skopje, Republic of Macedonia. For statistical data analysis we used Chi-square test and Fisher exact test with level of significance p<0.05.

Results: Pathologic audiograms were classified in 5 types: 0.8% were Type I (slope at 4000 Hz); 15.1% were Type II (slope at 2000 Hz); 67.4% were Type III (notch at 4000 Hz); 0.8% were Type IV (notch at 2000 Hz), 8.9% were Type V (flat) and 7% were out of this classification. In patients with positive noise history 79.2% had audiometric notch. Unilateral notches at the left ear were the most frequent; 91.8% of the patients with notched audiogram were with and 8.2% without positive noise history.

Conclusion: Audiometric notch is not a pathognomonic sign of NIHL. It can occur in absence of positive noise history. There is a need of unique definition of audiometric notch. Further studies could focus on hearing conservation programs.

#### AUDIOMETRIC FINDINGS IN PATIENTS WITH SUBJECTIVE TINNITUS

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Aim: To determine the prevalence, type and degree of hearing loss in patients with subjective tinnitus and to analyze the quality features and some tinnitus characteristics related to associated hearing loss.

Methods: We analyzed audiometric, otoscopic findings and case history of 702 patients, 376 males (53.6%) and 326 females (46.4%), aged 19 to 89 years. The patients were examined at the Department of Otorhinolaryngology, City General Hospital "8-September", Skopje, Republic of Macedonia, during the period of January 2014 to December 2014. For statistical data analysis we used Chi-square test with level of significance p<0.05.

Results: Most of the patients were males at the age 60 to 69 years (12.8%), but there was no significant difference in age and gender distribution (p=0.448). Bilateral tinnitus was most common (59.3%). Unilateral tinnitus was more common in the left ear (59.1%). Prevalence of hearing loss among tinnitus patients was 92.7%; 7.3% had normal hearing. Hearing loss at high frequencies was most common (p<0.00001). Most common otologic conditions were acoustic trauma and noise induced hearing loss. Most of the patients described their tinnitus as high-pitch whistling, had bilateral tinnitus and bilateral sensorineural hearing loss.

Conclusion: Most of the patients with subjective tinnitus have some degree of hearing loss. There is a need of performing extended high-frequency audiometry in tinnitus patients with normal hearing at standard pure tone audiometry.

Key words: tinnitus, hearing loss, normal hearing.

## **CANAL DEHISCENCE**

#### SEMICIRCULAR CANAL MALFORMATIONS: CLINICAL AND INSTRUMENTAL FINDINGS

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Anomalies involving only the semicircular canal (SCC) are classified as a mild inner ear malformation. Among these the lateral SCC dysplasia (shortening and widening) is the most frequent. . The results of several studies have not shown any consistent relationship between SCC malformations and hearing loss. As for cochlear function, few reports have examined the vestibular symptoms and any correlation between the severity of the canal and the vestibule malformations and vestibular impairing exists. The purpose of our study was to describe the cochleo-vestibular assessment in patients with sporadic semicircular canal malformations and to suggest possible explanations for the variability of symptoms and signs induced by SCC anomalies. The study was performed in 22 adults patients affected by lateral semicircular canal dysplasia identified in the ENT and Audiology Unit of the University of Bologna from January 2010 to December 2014. All patients were examined by means of appropriate temporal bone high resolution computed tomography (HRCT) study with multiplanar reconstruction and were screened to exclude central nervous system and eighth cranial nerve enhancing lesions using contrast-enhanced brain magnetic resonance imaging (MRI). A careful anamnestic evaluation and a full audio-vestibular test battery were attempted for each patient (pure tone audiometry, infra-red videonystagmoscopy (head pitch test, Hallpike maneuver, bilateral mastoid 100 Hz-vibration, head shaking test and Valsalva maneuver with pinched nostrils), bithermal caloric test, cervical and ocular vestibular evoked myogenic potentials study (air and bone conducted stimuli), head impulse test using video-HIT in the planes of all 6 semicircular canals). All the patients bilaterally had the SCC malformation: 15 of 22 patients had bilateral lateral SCC dysplasia; 3 patients had left LSCC dysplasia and right LSCC aplasia; 1 patient had aplasia LSCC bilaterally; 1 patient had SCC dysplasia of all 6 SCC; 1 patient had posterior SCC aplasia and contralateral posterior SCC dysplasia; 1 patient had LSCC dysplasia and anterior arm superior SCC aplasia. None of the patients had cochlear malformations or enlarged vestibular aqueduct. No external ear, middle ear or ossicular abnormalities were noted on imaging. 6 of 22 patients had Meniere-like clinical history. We will describe in detail the cochlea-vestibular instrumental findings.

### SUPERIOR CANAL DEHISCENCE MAY INDUCE ENDOLYMPHATIC HYDROPS: PHYSIOPATHOGENETIC CONSIDERATIONS ABOUT THE "SPONTANEOUS PLUGGING PROCESS" THEORY

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Besides typical symptoms and signs (including pulsatile tinnitus, hyperacusis, pressure/sound induced torsional nystagmus, conductive hearing loss and lowered thresholds of air-conducted VEMPs) an analysis of the literature reveals a certain clinical polymorphism induced by superior canal dehiscence (SCD). In addition to asymptomatic persons or subjects presenting with cochlear disorders as the only symptoms (partly explained after the introduction of the "near-dehiscence syndrome"), cases where atypical Ménière-like crises represent the most prominent clinical features have been recently described. Despite of all, no unanimous interpretation for all these different phenotypic patterns has yet been offered. Additionally, if surgical occlusion of the superior canal (SC) has demonstrated to result in SCD symptoms control inducing a selective SC dysfunction, it is common finding for practitioners to detect a reduced SC angular-VOR gain in asymptomatic patients with wide-sized dehiscence. These findings led authors to propose the occurrence of a natural SC plugging realized by middle fossa dura prolapsing into the canal lumen. The compression of the membranous canal would result in a progressive endolymphatic blockage, selectively inactivating SC reflexes and excluding the dehiscent canal from labyrinthine micromechanics. We hypothesize that, in particular condition such as during sudden small intracranial pressure changes, a transient and partial herniation of dura through the dehiscent canal could induce a transitory hydropic condition of the inner ear, leading resulting in recurrent vertigo spells variably associated with cochlear symptoms. Analogous Ménière-like clinical pictures have already been registered in the first postoperative period in a considerable amount of patients with SCD who were submitted to canal occlusion. We conducted a retrospective review of the clinical records of 242 patients (114 M, 128 F, mean age 56.8 y, range 8 – 88 y) diagnosed at our institution as having a dehiscent or a an extremely thinned superior canal at least from one side at HRCT scans, and we selected 22 patients in whom a Ménière-like symptomatology (i.e. recurrent spontaneous vertigo attacks with "irritative" nystagmus and auditory symptoms) was detected. A subsample of patients with a complete otoneurologic assessment (audiometry, VOG eye recording, air/bone-conducted cervical/ocular VEMPs, caloric test, video head impulse test) was selected for supporting this emerging physiopathogenetic hypothesis.







## **CLINICAL ISSUES**

#### A NEW MENIERE'S DISEASE-SPECIFIC QUALITY OF LIFE SURVEY: DOKUZ EYLUL UNIVERSITY MENIERE'S DISABILITY SCALE

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Meniere's Disease is a chronic, non-life-threatening inner-ear disease, with attacks of disabling vertigo, progressive hearing loss. and tinnitus as major symptoms. All three symptoms, separately or in combination, cause great distress and have a considerable impact on the quality of life of patients. The aim of this study was to analyze the psychometric properties of Dokuz Eylul University Meniere's Disability Scale developed originally. 93 patients with definite Meniere's Disease included in this study. Dokuz Eylul University Meniere's Disability Scale and Dizziness Handicap Inventory were administered. 45 of patients were male, 48 were female and the mean age was 48.9 ± 12.1 years. Cronbach's alpha coefficient, p values of Tukey's additivity and Hotelling's chi-square tests, intra-class correlations coefficients, item-total correlations coefficients, Cronbach's if item deleted values were calculated. And exploratory factor analyses by Varimax rotation with Kaiser normalization and Goodness of fit confirmatory factor analyses were performed. Cronbach's alpha was 0.92, intra-class correlation value was significant (p <0.001). Both Tukey's and Hotelling's tests showed significancy (p<0.001). Results of the goodness of fit statistics showed that the expression levels of the items to the scale was high, and the relationships of item-scale were sufficient. As a result of this study, Dokuz Eylul University Meniere's Disability Scale is a valid and reliable scale.

#### ANALYSIS OF THE MOST COMMON CAUSES OF DIZZINESS.POSSIBILITY TREATMENT OF PATIENTS

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**Introduction:** A large number of patients in ENT clinics complain of dizziness as main symptom.

**Objective:** The objective of this study was to show the relationships which are most commonly diagnosed in adults (children are not covered in this paper) that is solely or primarily complain of dizziness, and to analyze the performance of standard therapeutic modalities.

Substances and Methods: A prospective clinical study of 60 patients, which the author examined and monitored in the six-month period. All patients gave their signed consent to participation in the preparation of this paper. A diagnosis of vertigo have set up on the basis of: audiological-vestibulatory history; otorhynolaryngologycal clinical examination and audiological-vestibulological tests. The statistical analysis of the results obtained were used nonparametric methods for testing the differences.

Results: The most common cause of vertigo is BPPV (50.8%), neuronitis n.vestibularis (16.9%), Meniere's Disease (15.3%), vertigo of central origin. BPPV is more common in women, in patients with a history of head injury, AUPV, migraine, surgical intervention (stapedotomy). In 80% of cases the affected semicircular canal, in 20% of cases affected by horizontal semicircular canal (geotropic variant hBPPV, more frequent), an extremely rare upper semicircular canal. Of reduction maneuver (CRP) successful in 87.5%, Gufoni maneuver successful 71% of the cases. Patients with acute unilateral peripheral vestibular deficit recovering an average of 3 to 4 weeks depending on the localization of damage, the nature of the pathological process, changes in the CNS, vascular and general diseases.

**Conclusion:** Damage to the peripheral vestibular apparatus are by far the more common, and most of them BPPV. The most common form of BPPV is a canalolithiasis of semicircular canals, accounting for about 30% of all dizziness. The success of the CRP without transition to another form of BPPV's 87.5%.

Key words dizziness, classification, treatment.

#### ANXIETY AND THE SEVERITY OF THE SYMPTOMS IN PATIENTS WITH MENIERE'S DISEASE

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Meniere's Disease symptoms include vertigo, hearing loss, tinnitus and aural fullness which can be extremely stressful and limiting in everyday life. Meniere's patients also reported symptoms of anxiety and depression, worse social functioning and physical pain. The aim of the study is to determine is the severity of the Meniere's Disease symptoms correlated with anxiety in patients, depending on the age of the patient, duration of the disease and daily doses of betahistine. The study included 37 patients diagnosed with Meniere's Disease (28 females and 9 males) of an average age of 46.2 years. Duration of the disease varied from 6 months to 5 years. 34 patients were on therapy with betahistine (daily doses from 48 to 144 mg) and 3 were without any therapy. During 12 weeks (from January to March 2014) patients filled out Meniere's Disease Functional Level Scale and Zung Self-Rating Anxiety Scale every week. There was significant positive correlation in scores variation of Meniere's Disease Functional Level Scale and Zung Self-Rating Anxiety Scale though the duration of the study (Pearson's correlation, p<0.05). Scores were significantly higher in older patients with longer duration of the disease, and they weren't influenced by daily doses of betahistine.

#### AUDIOVESTIBULAR FINDINGS IN CEREBELLOPONTINE ANGLE TUMOR

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Acoustic tumors are benign schwannomas of the eighth cranial nerve. Acoustic tumors most frequently arise in the cerebellopontine angle. So far there are a number of studies being published about the audiometric findings in the patients with acoustic tumor. However, few studies have been done about the other cerebellopontine angle tumors. This study retrospectively evaluated the difference between audiovestibular findings of acoustic tumors and the other tumors.

Eighty two patients with unilateral cerebellopontine angle tumor were involved in this study. Fifty patients had the acoustic tumor (AT) and 32 patients had the other tumors (non-AT). Thirty patients were male and 52 were female. Forty three cases were right side and 39 cases were left side. The mean ±SD age was 43.7±12.1 years at the time of initial examination. For all patients, diagnosis was made by preoperative MRI and confirmed pathologically after surgery.

Before surgery, the patients underwent pure-tone audiometry (PTA), speech audiometry, distortion product otoacoustic emission tests (DPOAE) tests, caloric ENG, and vestibular evoked myogenic potential (VEMP). PTA was evaluated as the mean of thresholds at the four frequencies (250, 500, 1000, and 2000Hz). We divided the patients into two groups according to speech discrimination scores (SDS), greater than 80% and less than 80%. DPOAE was measured using ILO292-USB (Otodynamics model).We defined the amplitude of 5 dB SPL above the level of the corresponding noise floor as DPOAE positive. The preoperative and postoperative findings were compared. Tumor size was measured as the largest diameter on axial, coronal, or sagittal MRI views. The Fischer test was employed to test the correlation of PTA, SDS and DPOAE abnormality between AT and non-AT. The mann-whitney U test was used to identify the relationships between tumor size and PTA, SDS, DPOAE. A P-value of less than 0.05 was considered to be statistically significant. The preoperative PTA was normal in 39 cases (47.6%), SDS was more than 80% in 44 cases (55.7%), DPOAE was normal in 42 (51.9%). The tumors size were from 7 mm to 58mm. The mean ±SD tumor size was 29.3 ±10.9mm. PTA and DPOAE were significantly better in non-AT than those of AT. SDS was not significantly different between AT and non-AT. The preoperative PTA and SDS in AT were significantly worse when the tumor was huge. There were no statistically different findings between tumor size and DPOAE in AT. There was no correlation between the preoperative PTA and tumor size in non-AT. However, the statistical difference was noted between SDS, DPOAE and tumor size in non-AT. The results of PTA, SDS and DPOAE were normal with half of non-AT It is important to differentiate AT or non-AT before surgery for the prediction of the hearing after surgery. The cerebellopontine angle tumor with the DPOAE negativity and severe hearing loss might indicate AT. The tumor which size is large and normal hearing might be non-AT. PTA, SDS and DPOAE have an important role for prediction of tumor location. The location of non-AT may affect the audiovestibular findings.



#### BENIGN PAROXYSMAL POSITIONAL VERTIGO FOLLOWING STAPEDOTOMY

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#### Introduction.

It is well documented in literature that certain percent of post-stapedotomy patients experience bouts of vertigo in postoperative period. In some of these patients Dix-Hallpike maneuver is positive, and the diagnosis of benign paroxysmal positional vertigo can be made. While exact incidence of this phenomenon still remains unknown, the pathophysiology seems to be clearer, as it is regarded to be the consequence of utricular trauma during the operation.

Patients and methods

Case series. The author presents case series of the patients with benign paroxysmal positional vertigo, which occurred during the following year after stapedotomy operation. They all responded well to treatment with reposition maneuvers, and remained well during the follow-up period of three years.

Conclusion.

Several authors reported stapedotomy, as well as stapedectomy operations, as etiological factors for benign paroxysmal positional vertigo. Reported incidence in one study is high, 8.5%. It is also stressed that correct measurement of distance between incus and stapes is essential for avoiding this phenomenon. Nonetheless, it remains of utmost importance to warn the patients about this condition, and to differentiate it in timely manner from other causes of post-stapedotomy vertigo.

#### CONSERVATIVELY MANAGED SPORADIC VESTIBULAR SCHWANNOMA: AUDIOVESTIBULAR FACTORS INFLUENCING QUALITY OF LIFE

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Introduction: The objective was to evaluate the quality of life (QoL) of patients with conservatively managed Vestibular Schwanommas (VS) and describe their sociodemographic characteristics.

Methods: The questionnaires were answered by patients via a newly developed website using a unique token. Those who did not accept or understood answering via the internet had a second possibility of a paper version, which were send to them by post. They were asked to return their completed questionnaires in a prepaid envelope.

Results: 87.7% response rate (994/1133). The questionnaires included Short Form 12 Health Survey Version 2 (SF-12v2), the Hearing Handicap Inventory (HHI), Tinnitus Handicap Inventory (THI), Dizziness Handicap Inventory (DHI), The Penn Acoustic Neuroma Quality-of-Life Scale (PANQOL scale), and questions on sociodemographic characteristics. 898 patients reported hearing loss (95.8%). Six hundred eighty four reported tinnitus (72.9%) and 463 reported imbalance (49.4%). Regression analysis showed that DHI score and age were strong predictors of physical component summary. DHI and THI scores were significant predictors of mental component summarv.

Conclusion: Dizziness is the most significant audiovestibular predictor of QoL in patients with VS. Tinnitus also has an impact on mental QoL. Hearing loss does not seem to influence QoL significantly. Other factors may have an important role to play in determining QoL

#### EVALUATION OF URINARY DEOXYPYRIDINOLINE LEVELS AND THEIR CORRELATION WITH TEMPORAL BONE HRCT AND DENSITOMETRIC DATA IN OTOSCLEROSIS

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Otosclerosis is a disease characterized by progressive hearing loss in one or two ears. Potential causes include genetic, endocrine, immune, viral factors and connective tissue diseases. It's suggested that in patients without a disease associated with bone resorption or increased bone metabolism (osteoporosis, osteogenesis imperfecta, Paget's disease etc.), supporting the diagnosis of otosclerosis with a non-invasive urine test may contribute to monitoring and rehabilitation of the patient, planning of the timing of surgery and may be used as a screening test for other family members. High-resolution computerized tomography (HRCT) is widely used to visualize changes in the otic capsule due to demineralization. However, patients who were diagnosed or had clinical otosclerosis may not have any hypodense regions even by densitometric measurements. Deoxypyridinoline (DPD) is a marker which is excreted by urine without metabolization and increases with bone resorption and osteoclastic activity. The urinary DPD level, a product of bone breakdown, isn't affected by the degradation of newly synthesized collagen and diet. It has been demonstrated that to have a high specificity to bone tissues and is virtually bone based. It's suggested that urinary DPD level may be a diagnostic marker informing the progress of the disease in patients with otosclerosis. Method: In our study, when evaluating data related to the urinary DPD, two groups were formed, including a patient group and a control group. Twelve patients surgical confirmed as having otosclerosis constituted the patient group. The patient group was further categorized into bilateral(n:7) and unilateral(n:5) after radiological, audiological and surgical assessments. Audiological data of 18 ears belonging to 12 patients were examined. Stapedectomy surgery was performed unilaterally in 11 ears of 12 patients, and in both ears of 1 patient. Patients were grouped according to positive or negative radiological focus detected by HRCT and densitometric measurements. Results: In patients with bilateral involvement, DPD values were seen to be significantly high although no radiological foci were observed. In the normal group, the mean value of urinal DPD ratios of patients with bilateral involvement was higher than the patients with unilateral involvement.bWhen, in the patient group, the correlations between the first and second urinal DPD ratios and otosclerosis were examined, a moderate correlation between the mean value of second urine DPD ratios and otosclerotic involvement (R=0,61) were found significant(p:0.03). All the patients who were diagnosed or having otosclerosis with the combined of urine DPD ratios and HRCT were surgically proven to have the disease. It was discovered that by adding urine DPD ratios to HRCT, sensitivity of the HRCT increased from 50% to 100%. Due to the low number of patients in our study, the value of DPD ratios in unilateral and cochlear otosclerosis cases couldn't be evaluated. In conclusion, diagnosis of the otosclerosis needs surgical confirmation and currently there are no other methods to evaluate the metabolic activity of otosclerotic foci except HRCT densitometry. However, our study showed that urine DPD ratio gives us an opportunity to support the diagnosis of otosclerosis in a non-invasive, low cost and quick way. Urinary DPD ratio can be a diagnostic marker and can inform about the disease progress and response to medical treatment in patients with otosclerosis.

### FORMS OF VERTIGO IN ENCLOSED TYMPANUM CHRONIC MASTOIDITIS

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The aim of this paper is to underline two types of vertigo which can be the clinical manifestations of enclosed tympanum chronic mastoiditis: prolonged vertigo, accompanied sometimes by hearing symptoms such as aural fullness or tinnitus and recurrent vertigo, lasting from several hours to a day, always accompanied by auditory manifestations (clogged ear or worsening hearing loss or tinnitus). The study was performed on a number of 13 patients who presented to the Emergency Room with acute vertigo. In crisis, clinical examination included: otoscopic exam, audiometric tests, vestibular examination; after overcoming the acute phase, the investigation protocol included pure tone audiometry, BERA (brainstem evoked response audiometry) acoustic immitance, VEMP testing, CT scan. 8 patients had prolonged recurrent vertigo lasting more than 24 hours; accompanied by otalgia, tinnitus, hearing within normal limits; 5 of them had various degrees of tubal dysfunction, from mild to severe; 3 of them had normal middle ear pressure. 5 patients had Meniere-like paroxysmal vertigo, lasting only a few hours, accompanied by tinnitus and hearing loss. All patients had tubal dysfunction in the affected ear. Chronic mastoiditis vertigo can sometimes simulate other clinical vertigo such as vestibular neuronitis or Meniere disease. Middle ear CT scan or X-ray in Schuller incidence can indicate the pneumatization of the mastoid air cells. In these cases, the surgical treatment represents the curative solution for hearing preservation and vertigo disappearance.





#### INTRAVESTIBULAR SCHWANNOMA: SYMPTOMATIC TREATMENT WITH INTRATYMPANIC GENTAMYCIN

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Objective- Intralabyrinthine schwannoma is a rare benign tumor that affects the ends of the cochlear and vestibular nerves. In the majority of cases it occurs with unilateral progressive sensorineural hearing loss. Less frequent symptoms include tinnitus, imbalance, vertigo or fullness. The advent of magnetic resonance imaging allows early diagnosis, which permits an appropriate therapeutic protocol. This report describes a unique case of intravestibular schwannoma, with fluctuating hearing loss and intractable vertigo treated with intratympanic gentamicin.

Patient/Intervention- A 28-year-old woman with intractable vertigo and fluctuating left- side hearing loss caused by left-side intravestibular schwannoma. She underwent spontaneous vestibular tests, pure tone audiometry, electrocochleography and Head Impulse Test. Since surgery was temporarily excluded to avoid hearing loss, a single dose of intratympanic gentamicin was therefore administered.

Main Outcome Measures- Effectiveness of treatment with intratympanic gentamicin in reducing symptoms of dizziness with hearing preservation.

Results- After intratympanic gentamicin treatment, the patient showed a significant improvement of her symptomatology with bilateral normoreflexia and moderate to flat sensorineural hearing loss.

Conclusion- Intratympanic gentamicin infiltration is a valid therapeutic option for patients with intralabyrinthine schwannoma affected by intractable vertigo, when hearing is still socially useful. It may provide excellent results on the vestibular symptoms, although a noxious effect on hearing is possible, without the possibility to stop the tumor growth. Therefore patients suitable for this treatment need accurate magnetic resonance imaging follow-up to monitor the development of tumor growth.

#### MANIFESTATION OF LERMOYEZ'S SYNDROME IN MENIERE'S DISEASE PATIENT

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Although Lermoyez's syndrome has been described already at the beginning of the 20th century there are not many cases found in the literature and not much is written about its etiology, diagnosis and treatment. Is there really such a low incidence or is the syndrome simply unrecognized? Some authors consider it as a variant of Meniere's Disease and some as a sole entity.

A 34-year old male with a history of a sudden hearing loss, tinnitus and feeling of pressure in the left ear was admitted to our hospital. On admission he had no vertigo and no spontaneous nystagmus was seen. His hearing on the right ear has been damaged for years. Audiogram revealed deterioration of hearing threshold in his left ear, a sensorineural hearing loss especially in the low frequencies. Tympanometry showed curve A on both sides. He was treated with oral corticosteroids and betahistine. During hospitalization patient noticed improvement of hearing in his left ear but at the same time vertigo with spontaneous nystagmus toward the affected ear had appeared. On examination he had no signs of ear infection. Check-up pure tone audiometry confirmed improvement of the hearing in the low frequencies from 125Hz-500Hz. MRI excluded pathologic changes in the brain, cerebellopontine angle and in the course of the vestibulocochlear nerve. Serology for Borrelia Burgdorferi and rheumatologic tests were negative. On follow up he complained of frequent day to day fluctuations of hearing threshold in the left ear. Usually before the vertigo attack his hearing improved and later spontaneous nystagmus towards the affected side was detected. As troubles with vertigo attacks, tinnitus, ear fullness and fluctuation of hearing had repeated several times we suspected of a variant of Meniere's Disease – Lermoyez's syndrome. He received an intratympanic injection of dexamethasone but it did not relieve his symptoms.

#### MENIERE'S DISEASE PRESENTED WITH MICRO VASCULAR COMPRESSION OF THE VESTIBULOCOCHLEAR NERVE

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Objective: The Aim of the presentation is to report the controversy on management of the neurologic disease of neurovascular compression of the eighth cranial nerve.

Case presentation: A 41 year-old-woman who is a teacher at the University and a candidate for doctoral thesis, documented for 4 years with Meniere's Disease, having symptoms of disabling vertigo, tinnitus, aural fullness and hearing loss on the left side. After failure of medical treatment, surgery was suggested. The patient decided to go ahead with the operation, due to the negative influence of the vertigo and tinnitus on her quality of life.

MRI of the brain didn't show any abnormality but MRI angiography showed a left loop compression of the anterior inferior cerebellar artery (AICA). Results: A Retrosigmoid approach was performed. Intraoperative findings proved the radiologic findings. The AICA loop was mobilized and Teflon pad was interposed and separated from the vestibular nerve. Neurotomy of the vestibular nerve was carried out.

The patient's symptoms resolved after surgery with a follow-up of 5 years. Conclusion: In the management of Meniere's Disease, MRI should include sequences that are capable of demonstrating vascular anomalies in patients with persistent tinnitus and vertigo.

The rate of success of surgical decompression is satisfactory. However, it is still difficult to consider neurovascular compression of the eighth cranial nerve as a major cause of disabling vertigo and tinnitus.

#### OTITIS MEDIA AND MENIERE' S DISEASE

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Meniere's disease is a vestibular disturbance with a incidence of 12/1000 people all over the world, characterized by vertiginous attacks, sensorineural hearing loss, tinnitus and ear fullness. These symptoms, vertigo being the most distressing, are caused by the presence of endolymphatic hydrops. Etiopathogenesis of disease include a various factors as: congenital, trauma, infection/ inflammation, immunological, biochemical, genetics and others. However, nature of all mechanisms of endolymphatic hydrops is still unclear. Histopathological temporal bone studies have shown a different changes on the structural elements of inner ear. Because of that, definitive curative treatment for Meniers disease does not currently exist and the therapeutic procedure is mainly aimed at relief of vertigo, that in the majority is most distressing symptoms. Frequently, we have seen the patients with symptoms of Meniere's Disease who had previously some form chronic otitis media (active or inactive), with or without complications. Association of otitis media and Menier s disease is interesting for differentiation of nature disease as cause-sequence. The purpose of our paper is to present the result our clinical studied on consequently treating the patients with otitis media and associated Meniere's disease. We analysed an influence of potential factor of chronic inflammation of the middle ear to occurrence of Menier s disease, but also, for clinical manifestation, diagnosis and treatment. We believed that long standing middle ear inflammation may influence on pathogenesis of Meniere's Disease with importance for diagnosis and treatment of diseases.



#### PSYCHOLOGICAL EVALUATION OF THE PATIENTS WITH VERTIGO DUE TO OTOLITH ORGAN

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Introduction: The otolith function has been able to be evaluated by vestibular evoked myogenic potential (VEMP), then a new clinical entity as disequilibrium due to the otolith dysfunction has been established. Some cases of them complained of severe psychological problems. We studied the psychological examinations for the patients with otolith vertigo.

Subjects and a Method: Subjects were 19 patients who were diagnosed as vertigo due to otolith organs. The tentative diagnostic criteria for otolith vertigo is following; 1) the complaint was of non-rotatory disequilibrium. 2) Abnormal results were shown on cVEMP and/or oVEMP. 3) There were no abnormal results from routine examinations. 4) There were no cerebellar signs or intracranial lesions detected by brain MRI. Their psychological conditions were evaluated using Cornel Medical Index (CMI), State-Trait Anxiety Inventory (STAI) and a self-evaluation dejection standard (SDS). In addition, 13 patients with benign paroxysmal positional vertigo (BPPV) and 27 patients with Meniere's Disease were also evaluated.

Result: Abnormal results on CMI (category 3 and 4 on Fukamachi's classification) were shown in 58%. 15% and 37% of the subject with otolith vertigo, BPPV and Meniere's Disease respectively. The subjects with otolith vertigo resulted in higher state anxiety than trait anxiety in STAI. Depressive tendency (>48 in SDS) was shown in 20%, 38% and 33% of subjects with otolith vertigo, BPPV and Meniere's Disease respectively.

**Consideration:** The high anxiety in the subjects with otolith vertigo may originate from the recurrence of symptoms without trigger and diagnose as the unknown origin in another clinic. Their daily livings were not limited thus the tendency of depression was less in the subject with otolith vertigo.

#### RELATIONSHIP BETWEEN CLINICAL PROPERTIES AND AUDIOVESTIBULAR FINDINGS IN PATIENTS WITH MENIERE'S DISEASE

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Meniere's Disease (MD) is characterized by endolymphatic hydrops. The aim of this study was to analyze the relationship between audiovestibular findings and history of patients with MD. ENT examination, clinical history and audiovestibular evaluations were performed in 93 patients with definite MD. Forty five patients were male, 48 were female and the mean age was  $48.9 \pm 12.1$  years. The mean duration of MD was 5.6 years. The mean 0.5-2 kHz and 0.5-3 kHz air conduction hearing thresholds were 46.8±21.4 dB HL and 47.4±22.3 dBHL, respectively at the pathological side of unilateral MD patients (n:87). In bilateral cases (n:6), these values were  $58\pm14.4$  dBHL and  $54.8\pm19$  dBHL, respectively at the right side;  $46\pm14.7$  dBHL and  $49.5\pm21.4$  dB HL respectively at the left side. Vestibular function test findings including eyes closed tandem gait, sharpened Romberg and Unterberger tests were encountered abnormal over 50% of the patients. In videonystagmography, saccadic and tracking eye movements were found as abnormal in 5% of them. Spontaneous nystagmus was detected 15% and bi-thermal caloric test showed 50% canal paresis of the involved ear of the cases. Patient age was found to be significantly positively correlated with audiological findings and the attack severity; older patients had significantly worse hearing thresholds and more severe vertigo attacks. There was also a strong positive correlation between the caloric responses and audiological findings of the involved ears. The hearing status of the non involved side was significantly correlated with the attack duration and presence of headache. It was concluded that audiovestibular findings in addition to a detailed history is necessary to obtain the sufficient information about the clinical features of MD in each patient.

### REVERSIBLE INNER EAR SYMPTOMS IN DESTRUCTIVE TEMPORAL BONE LESIONS

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Temporal bone lesions are classified as malignant or non-malignant. They usually present as destructive lesions, mimicking chronic otitis media. Inner ear symptoms, both Meniere-like vertigo and sensorineural hearing loss are infrequent initial manifestations of these lesions.

Two case studies of patients with infected temporal bone lesions which developed gradually, diagnosed initially as a 'Menière'slike' attacks are presented. Eventually, these two patients were diagnosed histologically with Pagetoid lesion and Langerhans cell histiocytosis. The patients presented with newly onset acute debilitating vertigo and sensorineural hearing loss. Imaging revealed an extensive mastoid involvement with destruction of the semicircular canals. Both patients underwent surgical management for diagnosis and infection disease control, in face of the unusual presentation and in order to prevent further inner ear damage. Post operatively, the infection was controlled together with gradual resolution of the vertiginous symptoms, and an unexpected significant improvement of the sensorineural hearing loss. Follow up imaging revealed radiological resolution with re-mineralization of the otic capsule destruction and near normal radiologic appearance of the semicircular canals

### SLEEP AND DIZZINESS HANDICAP INVENTORY PROFILES IN MENIERE'S DISEASE AND VESTIBULAR NEURONITIS

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Introduction: Meniere's Disease has been associated with a high incidence of sleep disorder. Given lifestyle differences between patients with Meniere's Disease in metropolises, such as Tokyo, and those in local cities, such as Kochi, it is necessary to examine the sleep profile of Meniere's Disease patients in local cities. This report provides the results of a sleep survey conducted on patients with Meniere's Disease in Kochi City.

Patients: The survey was carried for 44 patients with Meniere's Disease and 11 patients with vestibular neuronitis treated at our hospital on an outpatient basis who completed the following: 1) a sleep questionnaire, and 2) the Dizziness Handicap Inventory (DHI) between February and April 2015.

### Survey items:

1) Sleep questionnaire: sleep time, sleep regularity, and the use of regularly used sleeping pills 2) DHI: the mean number of questions answered "yes" per patient and questions commonly answered "yes" by patients **Results:** 

1) Sleep guestionnaire: There were no significant differences between disease groups in terms of sleep time, sleep regularity and status of use of sleeping pills.

2) DHI: There was no significant difference in the mean number of questions answered "yes" between disease groups. The questions most commonly answered "yes" were Nos. 2, 11, 12 and 18 by patients of both disease groups; Nos. 3, 6, 9 and 24 by patients with Meniere's Disease; and Nos. 4 and 21 by patients with vestibular neuronitis. Discussion: We chose vestibular neuronitis as a comparator of Meniere's Disease. DHI: Patients with Meniere's Disease commonly answered "yes" to questions No. 3, 6 and 9, suggesting that they were anxious about unexpected onset of dizziness. This answer pattern also indicates their feeling of "lacking the sense of responsibility" due to dizziness, which is consistent with a common character trait of patients with Meniere's Disease. Sleep questionnaire: Kochi City is a city with a population of 300,000 in Kochi Prefecture, which has a total population of 800,000. The majority of the population consists of those engaged in primary industry, such as agriculture and fishery, suggesting a different lifestyle compared to metropolises. We thus speculate that this lifestyle difference affects sleep profiles. Conclusion: DHI results revealed a common character trait of patients with Meniere's Disease as reported previously. The results of the sleep questionnaire suggest different sleep disorder profiles between patients with Meniere's Disease in metropolises and those in local cities like Kochi City.



#### THE MANY FACES OF MIGRAINE - AUDITORY AND VESTIBULAR PRESENTATION: A CASE STUDY

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Migraine is characterized by diversity in clinical presentations, which sometimes represent a significant clinical dilemma. This is a case study of a 48 year old man (MN) who prior to the audio-vestibular assessment had been extensively investigated by the neurology and cardiology teams for unexplained "blackouts" - sudden loss of consciousness (LOC). He also had 2 episodes of right hemiparesis. Neurological investigations included EEG, carotid doppler, tilt table test and CT/MRI brain and cardiologic investigations 24 hr ECG, transthoracic echo and a reveal implant, with no abnormality identified. Audiovestibular presentation. MN was referred to Audiovestibular clinic for hearing loss 4 years after initial LOC. MN had hearing difficulty, intermittent tinnitus and marked loudness discomfort, greater on the left. A detailed description of LOC was obtained: LOC occurred suddenly, on average once a month, sometimes while sitting, usually in crowded and noisy places, preceded by a brief feeling of everything being "bright and loud", followed by LOC for a few minutes and a feeling of nausea and dizziness up to 2 days. He also had episodes of nausea and dizziness at night and on waking in the morning, as well as dizziness and disorientation in visually challenging situations. In addition, he had intermittent left "stabbing" headache. Family history was positive: 2 of 3 his brothers were affected by migraine. The clinical examination revealed a strong visual dependency. The pure tone audiometry (PTA) showed a bilateral sensorineural hearing loss of flat configuration: right 30-40 dBHL, left 45-55 dBHL. Strong transient evoked otoacoustic emissions (TEOAE) were recorded on the right, while only the high-frequency responses were recorded on the left. The caloric test showed a significant left directional preponderance (41%) and non-significant right canal paresis (13%). Sinusoidal and rotational tests applying videonystagmography showed left directional preponderance. Visual enhancement of the vestibulo-ocular reflex (WOR) was significantly high; the VOR suppression was normal. Vestibular evoked myogenic potentials were absent on the left, while there was a low VEMP threshold on the right.

Results interpretation. The elevated PTA thresholds in the presence of TEOAE were suggestive of a significant auditory dysfunction, greater on the left and at the lower frequencies. The vestibular findings were suggestive of a dysfunction with a significant asymmetry and increased vestibular sensitivity. A vestibular dysfunction has led to visual dependency.

Diagnosis and treatment. Migraine-related auditory and vestibular dysfunction, greater on the left, was suspected. MN received migraine prophylactic treatment, following which his hearing on the right returned to normal and the left to nearly normal (25 dBHL). The frequency of dizziness has significantly decreased and he had no further LOC.

Discussion. It appears that the semicircular and otolith systems were affected in different ways on the left (worse) side: while the otolith system appeared depressed, the sensitivity of the semicircular system seemed increased. The auditory function appeared affected in a similar way as the otolith system, by depression. These findings reflect the complexity of the inner ear control mechanisms, particularly of the vestibular system. The interface between mechanism of migraine and the control mechanisms of auditory and vestibular systems will be further discussed.

#### THE RISK OF MISDIAGNOSIS BETWEEN CHRONIC SUBJECTIVE DIZZINESS (CSD) AND MENIERE DISEASE (MD): A PSYCHOMETRICS ANALYSIS

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Chronic subjective dizziness (CSD) is a neurotologic disorder of persistent non-vertiginous dizziness or unsteadiness that is present throughout the day for 3 months or more and it may persist for years. Symptoms may be exacerbated by upright posture, patients' own movements, exposure to full field visual stimuli, or performance of precision visual tasks. CSD is usually triggered by neurotologic or other events that cause acute attacks of vertigo, unsteadiness, or dizziness, such as vestibular neuritis or panic attacks. The pathophysiologic processes underlying CSD are unknown, but may relate to patients' failure to return to normal postural control after adapting to the demands of acute vestibular crises. CSD was rarely seen with Ménière Disease (MD). Our study starts from several experiences on psychological factors in patients with CSD that suggested that preexisting anxiety or also anxiety diathesis may predict development of CSD symptoms after acute neurotologic illnesses. In contrast, patients with greater resilience, life satisfaction, and sense of coherence were less likely to develop CSD-type symptoms after acute neurotologic illnesses than individuals with lower score on these positive characteristics. Our aim was to compare MD and CSD patients and healthy controls (HCs) searching for psychometrics elements that can improve our diagnostic ability, reducing the risk of misdiagnosis and confusion between CSD and MD patients, especially in MD's intercritical phase. Participants were recruited from the Audiology and Phoniatrics Unit of Magna Graecia University, Catanzaro. We recruited 59 subjects: 19 CSD, 15 definite MD and 25 healthy controls, All patients underwent a clinical and instrumental evaluation including: 1) detailed history related to dizziness/vertigo; 2) self-reports of impairment on the Dizziness Handicap Inventory (DHI); 3) vestibular laboratory testing; 4) imaging with cerebral gadolinium enhanced MRI, if indicated; 5) psychometric evaluation with some guestionnaires Generalized Anxiety Disorder Seven-Item (GAD7), Nine-item Patient Health Questionnaire (PHQ9), Revised NEO Personality Inventory, (NEO-PI-R). Groups were comparable for demographic (age and sex) variables and state anxiety. A trend of difference was found in state depression (p=0.06) and it was driven by a higher scores in the CSD and MD groups relative to HCs. The two groups of patients were comparable for dizziness severity (p=0.71). Significant differences emerged in 3 groups in personality scores in Neuroticism, Openess and Conscientiousness (p's 0.004, 0.01 and 0.03 respectively). Most of these differences were driven by the comparisons between HCs and CSD groups and/or between HCs and MD groups, with low differences between CSD and MD groups. This allows us to suggest a possible common psychological ground in the two groups. in local cities like Kochi City.



#### TINNITUS AND SPONDYLOARTHROSIS: A STRONG CONJUCTION BETWEEN ENT AND REUMATOLOGY

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Aim: evaluate the role of a coexisting spondyloarthrosis and a bilateral hearing loss, due to age or other related systemic pathologies in a common complaint as tinnitus

2. a good conjunction between an ENT and a reumatologist would improve the complain of tinnitus although we know that it will never disappear completely. We have taken under consideration 30 patients between 65-70 years old complaining of: bilateral tinnitus, bilateral hearing loss, dizziness, cephalalgia and difficulty in moving the posterior part of the neck.

After a normal otoscopic exam, we performed an audiometry showing a middle to severe bilateral hearing loss due to age other sistemic disorders, or work, normal timpanometry. Than we performed a consult with the neurologist, she did not find any neurological problems.

The patients complain, that their tinnitus became worst while moving the neck, bending, or while atmospheric pressure due to bad weather changed.We performed a consult with the rheumatologist, after the x rays of the neck examination he found: cervical spondyloarthrosis of the posterior part of the spine with degenerative processes and osteophytosis.

Medication: AINSD, analgesics, physiotherapy, as well as vasodilatators and vitamin therapy to improve tinnitus. Both these therapies for all of our patients improve the tinnitus and they complained less although tinnitus did not disappear completely.

**Conclusion:** knowing that tinnitus is the most common complain of the third aged patients that sometimes causes neurosis as well we have to do our best to improve it and in our study a good conjunction between ENT and rheumatologist made it real.

## **COCHLEAR IMPLANT**

#### COCHLEAR IMPLANTATION AS A METHOD OF REHABILITATION OF TINNITUS

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Introduction: About 86% of patients with profound hearing loss tinnitus bothers. Cochlear implantation is the most effective method of rehabilitation of deafness in the modern world.

Aim: To evaluate tinnitus patients after cochlear implantation, depending on age, duration and etiology of deafness. Methods: We examined 384 patients aged 14-72 (years) (237 women and 145 men) with profound sensorineural hearing loss and tinnitus complaints. Cochlear implantation was performed in all cases. Unilateral implantation was performed in 376 patients, bilateral in 8 patients. The severity in patients experiencing ears was assessed using a visual analogue scale before implantation, the first fitting sound processor, and 6 months after the initial fitting. We analyzed the dependence of severity of tinnitus patients age, duration and etiology depending cochlear deafness prior to implantation.

Results: At 6 months after the first fitting 2% of tinnitus disappeared, 81% of patients with tinnitus patients has decreased, but not disappear, and 16% of tinnitus patients remained unchanged, and 1% of patients tinnitus has increased. Tinnitus significantly decreased in the majority of patients of all ages, etiology and duration of deafness before the cochlear implant.

**Conclusions:** Thus, Cochlear implantation reduces the severity of tinnitus in patients with profound sensorineural hearing loss. In addition to the effect of habituation, reducing tinnitus may be due to acoustic masking and direct stimulation of the auditory nerve. This observation was confirmed by the cochlear implant as an effective treatment for patients with single-sided deafness and severe tinnitus.

#### COCHLEAR IMPLANTATION IN A PATIENT WITH PAGET'S DISEASE

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Paget's disease (also known as: osteitis deformans) is the second most common metabolic bone disease, characterized by increased bone turnover with osteoclastic phase, followed by mixed phase and exaggerated osteoblastic (sclerotic) phase. This results in painful bony lesions, as well as hyperuricemia, hypercalcemia, cardiovascular, neurologic and neoplastic findings. Development of a significant hearing loss, as a result of changes in the mineral density of the Otic capsule, is often seen as well. We report a 59-year-old male with Paget's disease who suffered severe-to-profound hearing loss. The patient gained minimal benefit from conventional hearing aids and was referred to our center for cochlear implantation. Preoperative evaluation showed very poor communication skills, even relatively to his aided pure tone threshold and raised concerns regarding post-implantation outcomes. Nevertheless, the patient underwent cochlear implantation successfully. Follow up for nine months showed significant improvement. However, objective measurements using the Neural Response Telemetry (NRT) have not recorded any Electrical compound Action Potential (EAP) yet.

Since very few publications on cochlear implantation in Paget's disease were found in the literature, we wish to share our long term (6 years) clinical experience and hearing rehabilitation dilemmas involved in such a case in order to better predict the outcome in patients with Paget's disease following cochlear implantation.

#### FEATURES SOUND PROCESSOR SETTINGS IN PATIENTS AFTER ABI

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Introduction: In some cases, patients with bilateral deafness is impossible or inappropriate conduct cochlear implantation (in case of damage or auditory nerve aplasia, aplasia or significant ossification of the cochlea). For these patients, the auditory brainstem implant is created (ABI), which allows to stimulate the cochlear nucleus of the brain stem. In Russia the first 3 operations auditory brainstem implantation took place in December 2014 in cooperation with the Research Institute of St. Petersburg ENT, RNHI them. prof. AL Polenova, neurosurgical Clinic Fulda.

Aim: To study the fitting ABI, differences sound processor fitting cochlear implant and ABI. **Results:** During the operation, determined by the localization of the electrode array in the ventral cochlear nucleus by registering brainstem potentials to electrical stimulation (eABR) that have been registered in only one adult patient with neurofibromatosis 2. The second patient with neurofibromatosis 2 and a child with a cochlear aplasia eABR register failed. Connecting the processor ABI conducted in 1.5 months after operation. In adult patients, setting the parameters of electrical stimulation was carried out on their subjective feelings using scales assess the strength of the auditory and auditory sensations, as well as the patient's reactions to sounds and observations Speech-Language Pathologists. First connect the processor ABI the child was held in intensive care. In the future, the correction settings from the stimulation of the child conducted by behavioral reactions and observations Speech-Language Pathologists. During stimulation of individual electrodes, patients have no auditory sensations - vestibular, and other vegetative reactions. Electrodes, causing persistent side feeling increasing level of incentives were subsequently disabled. As a result, one patient 8 were activated electrodes in the 2 nd - 6 electrodes child - 7 electrodes. One of the adults observed inverted perception of pitch in the stimulation of the low- and high-frequency electrode, which is also taken into account when configuring the processor.

**Conclusion:** The development of auditory brainstem implant will allow for the rehabilitation of patients with hearing loss caused by not only the pathology of the inner ear and overlying part of the auditory pathway (aplasia of the auditory nerve, neurofibromatosis type 2, trauma of the inner ear and auditory nerve).





#### INNER EAR ABNORMALITIES IN COCHLEAR IMPLANT CANDIDATES

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**Objectives:** The purpose of this study is to analyze the inner ear abnormalities diagnosed in patients with bilateral profound sensorineural hearing loss, and to describe their surgical management.

Material and Method: We analyzed the imaging findings of 325 patients with bilateral profound hearing loss who were candidate for cochlear implantation in our department between June 2007 and December 2014. Radiological evaluation consisted for all the patients on High resolution computed tomography (HRCT) and magnetic resonance imaging (MRI).

**Results:** The age range was from 14 months to 65 years old. The majority of patients (85,5%) were of pediatric age group. Inner ear abnormalities were detected in 34 patients, among them 11(32,3%) were acquired, and 23 (67,6%) were congenital. Acquired abnormalities consisted on post meningitis ossification of the cochlea, which was complete and bilateral in 5 cases, an partial involving the basal turn in 6 patients. Of the inner ear congenital malformations, 9 (39,1%) patients had Mondini dysplasia, 3 (13%) patients had a Common cavity, 10 (43,4%) patients had enlarged vestibular aqueduct, and 1(4,3%) patient had a bilateral vestibular nerve and vestibule aplasia with normal cochlea.

Cochlear implantation was performed with adapted surgical procedure and electrode array. Patients with bilateral complete ossification of the cochlea, underwent auditory brainstem implantation.

**Conclusion:** Radiological imaging is an important part of the evaluation of sensorineural hearing loss. It contributes significantly to detect the abnormalities that could define the etiology of hearing loss, as well as to identify patients with a contraindication for cochlear implantation ,and those who require an adapted electrode array.

#### MIDDLE CRANIAL FOSSA VESTIBULAR NEURECTOMY FOR INTRACTABLE MENIERE'S DISEASE

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We conducted middle cranial fossa vestibular neurectomy (MCFVN) in two cases with intractable Meniere's Disease. During the surgery, both superior- and inferior vestibular nerves were easily identified through MCF window. Both vestibular nerves were completely sacrificed while leaving facial and cochlear nerves intact and there was no post-operative complications. After the surgery, the patients were relieved from vertiginous attack and their hearings were stable. They have continued the exercise program to promote vestibular compensation without any difficulties. According to these experiences, we would like to discuss the effectiveness and the safety of MCFVN for intractable Meniere's Disease in comparison to retrosigmoid vestibular neurectomy.

### OUTCOMES OF COCHLEAR IMPLANTATION IN CHILDREN WITH SEVERE AND VERY SEVERE MALFORMATIONS OF THE INNER EAR AND THE AUDITORY NERVE

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Objective: To describe outcomes after cochlear implantation (CI) of children with severe inner ear or auditory nerve malformations in an attempt to develop a more reliable outcome expectation scale and set standards of care in this group of pediatric CI candidates. Methods: A retrospective review, including 10 children with severe and very severe malformations of the inner ear and or the auditory nerve are included. Children with milder malformations e.g. EVA / Mondini were excluded. **Results:** Nine of the subjects developed speech awareness. One child developed spoken language prior to implantation and six after implantation. Of these six children, level of language was defined as adequate in two and they were enrolled in main stream education. Three of the ten children developed bacterial meningitis after implantation, in one, in whom the fundus of the inner ear was widely open and CSF leak recurred several times together with recurrent bouts of meningitis the implant was removed. In another child who developed bacterial meningitis (a recurrent episode) together with acute mastoiditis, it was necessary to remove the implant which was heavily involved in the purulent process. This child was implanted contra-laterally. One child with a very narrow auditory nerve does not use his implant.

Conclusions: Cl is a standard and successful procedure in most cases. In cases with severe malformation the procedure can be very challenging. Nevertheless the chance to develop sound awareness and even spoken language is good. It is critical to make sure that rehabilitation in this group is very intensive (far more intensive than in straightforward pediatric implantees) and medical follow is tight.

#### PERFORMANCE AFTER REVISION SURGERY FOR COCHLEAR IMPLANT SOFT FAILURES

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Introduction: Rate of cochlear implant (CI) device failure is very low, yet it is the most common cause for revision CI surgery. Device failure is very stressful for the patient and re-implantation should be performed as soon possible. A 'soft' Cl device failure is defined as a gradual decline in hearing function or the presence of non-auditory stimulation related to the CI. Aim: To evaluate resolution of 'soft' CI device failure symptoms after CI replacement. **Design:** A prospective study, including 24 recipients, mean age at  $CI = 9.0 \pm 13.8$  years (range, 1-60). Soft failures were categorized as: decline in performance (14), non-auditory stimulation (18) and combined conditions (9). **Results:** Following re-implantation, 22 recipients (92%) regained better CI usage, 13 recipients improved their speech performance, and non-auditory stimulation was resolved in 16 recipients. 8 recipients with combined conditions demonstrated improvement in both conditions. Average time from initial occurrence of problem to re-implantation was 2.02±2.01 years (range, 0.16-8.66). Discussion: The diagnosis of a 'soft' CI device failure is hard to make and therefore replacement of device in these cases is too often postponed. Today, a soft' CI device failure is absolutely confirmed only by improvement of symptoms after re-implantation. The results of the study show that most CI re-placements (92%) resulted in improvement of symptoms, yet in many of these cases the manufacturers could not detect the technological failure both prior to replacement as well as in the explanted device. Since all parties, implantees, clinicians, surgeons and manufacturers, are interested in replacing only the failed devices, and are absolutely not interested in replacing functioning devices, in order to shorten the time until re-implantation in cases of a suspected device failure, manufacturers should present more sensitive hardware diagnostic tools which will better correlate with the functional status of the patients.



#### PERSISTENT VESTIBULAR SYMPTOMS AFTER COCHLEAR IMPLANTATION – CLINICAL OVERVIEW

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Aim: Cochlear implantation is worldwide fully accepted method dedicated to patients with total or partial bilateral deafness. Nevertheless, vestibular and balance disorders are still one of the common complaints among the patients after the operation and while using the implant. According to the literature data, the percentage of vestibular symptoms ranges from 5,9% to 80% and that of vestibular examination abnormalities from 20-60%. Mostly, the symptoms are transient and in early postoperative period. The study aims at assessing the clinical reasons for persisting (lasting more than 2 months) vestibular disorders after operation that appeared directly or with delay after the operation.

Materials and Methodology: The retrospective study of patients after cochlear implantation, both through cochleostomy or round window approach (PDT-EC, PDT-EAS, PDT-ES).

**Results:** Persistent symptoms after cochlear implantation are rare. The most frequent reason for vestibular disorders is BPPV (benign paroxysmal positional vertigo) from the posterior semicircular canal, followed by vestibular hypo- or areflexia on implanted side. Other potential reasons like perilymph fistula, endolymphatic hydrops seems to be casuistic. The patients with BPPV show good response for repositioning maneuvers. Those with hyporeactiveness of vestibulum on implanted side were proposed vestibular rehabilitation.

**Conclusions:** Cochlear implantation may influence vestibular function and give persistent symptoms in rare cases. However, there are effective treatment options that may be offered for these patients.

#### **RESIDUAL HEARING IN CANDIDATES FOR COCHLEAR IMPLANTATION**

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Introduction: During the past two decades cochlear implant (CI) technology improved significantly, otologic surgeons worldwide have acquired the surgical skills needed and both surgeons and clinicians gained the confidence in the long term hearing results. The criteria for CI have been widen to include individuals with low frequency residual acoustic hearing whose speech understanding with hearing aids is insufficient and expected to improve with Cl. Hearing outcome of electro-acoustic stimulation has been proved to be better than CI alone due to low frequencies cues provided by the acoustic hearing. However, as of today, it is not possible to guarantee acoustic hearing preservation during CI surgery.

Objectives: To determine the amount of residual acoustic hearing in today's CI candidates in order to establish the effectiveness of the efforts invested in hearing preservation in cochlear implantation.

Material and Methods: Pre-implantation pure tone thresholds were assessed in 102Cl candidates who underwent Cl surgery between 2011 and 2013. All candidates were at least 11 years of age at surgery.

Results: At 250 Hz threshold were 80 dB or better in 41% of CI candidates and in 15% thresholds were 65 dB or better; At 500 Hz, threshold were 80 dB or better in 18% of Cl candidates older than 11 years and in 7%, 65 dB or better; At 1000 Hz, 2000 Hz and 3000 Hz threshold was  $\leq$  80 B in 7%; At 4000 Hz threshold was  $\leq$  80 dB in 5%.

Conclusions: A significant percentage of CI candidates are implanted while still having residual acoustic hearing in the ear planned for implantation. It is imperative to further refine the technology and surgical methods for hearing preservation during CI surgery.

### SETTING EXPECTATIONS FOR SPEECH UNDERSTANDING IN QUIET AND IN NOISE IN STRAIGHTFORWARD ADULTS COCHLEAR **IMPLANT CANDIDATES**

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Introduction: The huge amounts of cochlear implantation (CI) outcomes data collected over the last decades clearly show that in most CI recipients expectation are met. Nevertheless candidacy evaluation for CI remained somewhat cumbersome (and therefore expensive), even for the straightforward adult CI candidates.

Objective: To determine monosyllabic word recognition scores in a group of cochlear implantees who were considered straightforward candidates prior to implantation (normal language, fully involved in the hearing society, normal cochlea on imaging, no or minimal auditory deprivation prior to implantation), in an attempt to determine base-line values that can be used for future candidacy evaluation in similar candidates.

Patients: 30 experienced adult users of the type mentioned in the 'objectives' (defined as straightforward candidates prior to implantation by having normal language, full involvement in the hearing society, normal cochlea on imaging and no or minimal auditory deprivation prior to implantation).

Intervention: Patients were evaluated with the monosyllabic word recognition (AB) test at presentation level of 50dB HL with and without competing speech noise SNR +5dB (both the speech and the noise were presented at 0° azimuth). **Results:** The improvement on monosyllabic word recognition (HAB) after Cl was prominent. Prior to implantation the mean score on monosyllabic words averaged 25% in quiet and was much lower with background noise. After implantation it was 75% in quiet and 44% in background noise. When using also their contra-lateral HA, a significant further improvement was noted. Conclusions: Baseline values for the monosyllabic words scores in straightforward Cl users were established. These values can be used for predicting Cl outcome in similar straightforward adults Cl candidates by comparing their performance in the best aided condition to the scores achieved by the representing group of implantees assessed in the present study.



## **COMBINED TREATMENT**

#### COCHLEAR AND VESTIBULAR EFFECTS OF COMBINED INTRATYMPANIC DEXAMETHASONE AND GENTAMYCINE

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Intratympanic gentamycine is an effective treatment method for Meniere's Disease (MD). Unfortunately ototoxicity is a big drawback for gentamycine and it hinders its usage especially in patients with serviceable hearing thresolds or bilateral MD. The aim of this study is to evaluate cochlear and vestibular effects of intratympanic (IT) applications of gentamycine and combined dexamethasone + gentamycine treatments.

Twenty six female Wistar albino rats were divided into four groups as follows; group I (Control, n:6), group II (Dexametasone, n:5), group III (Gentamycine, n:7), group IV (Gentamycine + Dexametasone, n:8). On the first day of the study basal ABR (4 kHz, 8kHz, 16 kHz, 32 kHz) measurements were done. Then 0,02 ml intratympanic gentamycine(26.7 mg/ml) was applied in the anterosuperior portion of right tympanic membrane of the group III rats. A combination solution was prepared with the dilution of gentamycine in dexamethasone (with a final concentration of 13,35 mg/ml gentamycine and 2 mg/ml dexamethasone) then 0,04 ml of this solution was applied intratympanically in group IV and 0,02 ml of serum physiologic and dexametasone (4mg/ml) was applied respectively in groups I and II. On the 7th day of the study ABR measurements were repeated and vestibular functions were evaluated by airtight reflex, swimming and tail hanging tests. A blind observer rated these tests as 0 (normal), 1 (mildly affected) and 2 (severely affected). On the 21st day of the study, ABR and same vestibular tests were repated and animals were sacrificed to evaluate their inner ear structures at three levels( cochlea, vestibule and spiral ganglion) by light microscopy for histopathological changes and TUNEL staining for apoptosis.

In gentamycine group, hearing thresholds were deteriorated in all frequencies for both in early and late audiological measurements. In group IV at 7th day hearing thresholds were significantly better than group III except for 8 kHz. At 21st day group IV hearing thresholds were significantly better than group III in all frequencies. In group I and II hearing thresholds were not deteriorated in any of the measurements. According to observer, group III and IV vestibular function scores were higher than control groups both in 7th and 21st day measurements and there were no statistically significant difference between these two groups. Histopathological investigations revealed severe apoptosis in spiral ganglions, mild apoptotic changes in the cochleas and vestibules of group IIII. In group IV apoptotic changes in the spiral ganglion, cochlea and the vestibule were close to control group.

We observed that application of dexametasone with gentamycin led to a significant improvement in the hearing thresholds of rats. Although by subjective vestibular tests in both gentamycin and combination groups vestibulotoxicicity was present histopathological results showed no vestibulotoxicity in the combination group. Therefore we think that intratympanic application of dexametasone and gentamycin combination provides protection against ototoxicity by lowering the vestibulotoxic effect of gentamycine.

#### TRANSTYMYPANIC INNER EAR DRUG THERAPY

Aziz Belal Alexandria, Egypt

We started intratympanic drug therapy of Meniere's Disease in Alexandria, Egypt in 1993.

In light of the results of intratympanic therapy and the anatomical and operative observations of the presence of false round window membrane in almost 50% of the cases, we started transtympanic drug therapy: microscopic (2003) and endoscopic (2013). In this presentation, we describe the indications, equipment, rationale, technique, personal series and future directions.

## **ENDOLYMPHATIC SAC**

### CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR IN THE ENDOLYMPHATIC SAC OF THE RAT

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Aims and Introduction: In the endolymphatic fluid in the endolymphatic sac (ES), Na+ and CI- are dominant ions, and both are thought to be important for volume regulation. Na+, K+-ATPase at the basolateral membrane of ES epithelial cells provides the driving force for Na+ absorption. The Na+ flow is generally coupled with Cl- flow to neutralize the charge movement, thereby guaranteeing ionic neutrality. However, no chloride channels have been identified in the ES. Cystic fibrosis transmembrane conductance regulator (CFTR) is a plasma membrane cAMP-regulated CI- channel. The CFTR also acts as a regulator by exerting modulatory influence over the epithelial sodium channel (ENaC). In the ES, ENaC was identified in human and guinea pigs and shown to be localized at the apical membrane. The aim of this study was to examine the expression of CFTR in ES epithelia, which may play roles in the regulation of endolymph in the ES.

Methods: Four-week-old female Sprague-Dawley rats were used. Specific mRNA from ES epithelia was prepared using laser capture microdissection (LCM) and examined using RT-PCR. Localization of CFTR and ENaC in the endolymphatic sac was examined using immunohistochemistry.

Results and Conclusions: RT-PCR form the ES samples detected the expression of mRNA of the CFTR. Immunohistochemical analysis showed the expression of the CFTR on apical side of the ES epithelia and co-localization with the ENaC. These results suggest a pathway for CI-, possibly through interaction with the ENaC, which may regulate the endolymph in the ES.

#### HUMAN ENDOLYMPHATIC SAC AND COCHLEAR WATER CHANNELS- IMPLICATION TO INNER EAR FLUID HOMEOSTASIS AND MECHANISM OF MENIERE'S DISEASE

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Menières disease (MD) continues to defy and confound the clinical/scientific community more than 150 years after its original description. Already Guild (1927), Portman (1927), Hallpike and Cairns (1938), Yamakawa (1938) and Kimura and Schuknecht (1965) suggested that MD is caused by a dysregulation of endolymph. Yet, the mechanisms by which endolymph guantity and composition are regulated and the molecular mechanisms governing water permeation across the duct epithelium remain elusive. AVP/V2R complex may play a significant role in local fluid homeostasis. Immunohistochemistry suggests co-expressing AQP4 and AQP5 in human cochlea. AQPs were also found in human endolymphatic sac (ES) epithelia. However, results from human specimen are still rare comparing to animal study results. Human inner ear tissue was obtained at surgery in Uppsala University Hospital and subjected to immunohistochemical study. The study conforms to The Declaration of Helsinki and was approved by the medical ethical committee at the Uppsala University Hospital (2013). Patients consent was obtained. AQP4 and 5 were found in human cochlea as well as in the endolymphatic sac epithelia. V2R is also seen in the epithelia of human ES. The expression pattern of water channels in human cochlea is also presented.





#### PROX1 EXPRESSION IN THE ENDOLYMPHATIC SAC REVEALED BY WHOLE-MOUNT FLUORESCENT IMAGING OF PROX1-GFP TRANSGENIC MICE

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The transcription factor Prox1 belongs to the family of homeobox transcription factors. Prox1 is critical for organ development during embryogenesis and is involved in neurogenesis. Prox1 regulates differentiation of progenitor cells and initiation of neurogenesis. In the inner ear, Prox1 is expressed in vestibular hair cells, endolymphatic duct, and supporting cells in the embryonic stage but no longer detectable in the adult stage except in the spiral ganglion. The function of Prox1 in the cochlea and vestibule is thought to relate to the state of differentiation of the stem/progenitor cells. In the endolymphatic sac, the expression of Prox1 has not been reported.

Our recent study suggests that endolymphatic sac epithelial cells in the intermediate portion have sufficient Na+, K+-ATPase activity to provide the driving force for the Na+ transport required to absorb the endolymph. This active ion transport needs sufficient blood supply. In fact, several earlier reports have found many vessels in the endolymphatic sac. To further investigate the endolymphatic sac and associated blood vessels in more detail, three dimensional imaging of endolymphatic sac epithelial cells and vessels using confocal laser scanning microscopy or multiphoton fluorescence microscopy may be feasible, however, technical difficulties so far have prevented the optical sectioning through the temporal bone and the three dimension imaging of the endolymphatic sac.

In this study, we established a whole-mount imaging approach to directly visualize the endolymphatic sac, and examined Prox1 expression in the endolymphatic sac epithelia in adult mice.

Prox1-GFP BAC transgenic mice were deeply anesthetized, and were injected with 10 µL of tetramethylrhodamine labeled dextran intravenously. After 20 min, the mouse was perfused via the left ventricle with 4% PFA. The samples were fixed in 4% paraformaldehyde in PBS and decalcified in 0.12 M EDTA at 4 °C for 7 days. The temporal bone and the cochlea were examined using a 2-photon laser scanning fluorescence microscope.

The decalcified temporal bones and brain were embedded in OCT tissue compound. Sections were cut on a cryostat at -20 °C. Immunostaining was performed.

Results and Conclusions: Whole-mount imaging techniques through the decalcified temporal bone and three-dimensional observations of Prox1-GFP mouse tissue revealed the positive labeling of the endolymphatic sac in adult stage, and allowed, for the first time, the GFP-based identification of endolymphatic sac epithelial cells. Prox1 expression was observed in all parts of the endolymphatic sac epithelia. In intermediate portion of the endolymphatic sac, mitochondria-rich cells did not express Prox1, although ribosome-rich cells showed strong GFP labeling. The anatomical relationship between the endolymphatic sac and the surrounding vasculature was directly observed. In the endolymphatic sac, expression of Prox1 may suggest progenitor cell-like pluripotency or developmental similarity to systemic lymphatic vessels in other organs. This whole-mount imaging technique of the endolymphatic sac can be combined with other conventional histological, sectioning, and labeling techniques and will be very useful for future endolymphatic sac research.

#### THE HUMAN ENDOLYMPHATIC SAC IS AN INTRACRANIAL ENDOCRINE GLAND

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The function of the human endolymphatic sac has been enigmatic for decades. Several hypotheses have emerged however, including controlling endolymphatic fluid homeostasis as well as immunological defense of the inner ear. In addition, several studies give indications of a possible endocrine capacity and a yet undefined role in intracranial pressure homeostasis. However, as of yet, no direct evidence of such capacity exists. Accordingly, this study aims to explore and identify the hypothesized endocrine capacity of the human endolymphatic sac.

DNA micro-arrays and immuno-histochemistry were used for analyses of fresh human endolymphatic sac tissue samples. Twelve tissue samples from the human endolymphatic sac were obtained during translabyrinthine surgery for vestibular schwannoma. Microarray technology was used to investigate tissue sample gene expression, using adjacent dura mater as control. The expression of genes specific for an endocrine function was determined and results for selected key molecules verified by immuno-histochemistry. Several potent natriuretic peptides was found expressed significantly in the ES such as Uroguanylin and BNP, as well as peptides regulating vascular tone, including Adrenomedullin 2. In addition both Neurophysin and Oxytocin was found significantly expressed. All peptides were verified by immuno-histochemistry.

The present data support the human endolymphatic sac as an intracranial endocrine/paracrine gland with potent natriuretic capacity. Furthermore, the endolymphatic sac may influence the hypothalamo-pituitary-adrenal axis and may regulate vasopressin receptors and AQP-2 channels in the inner ear via Oxytocin expression. Thus, the endolymphatic sac is likely to regulate inner ear endolymphatic homeostasis through paracrine secretion of several peptides, but may also influence systemic and/or intracranial blood pressure through direct and indirect action on the vascular system and the kidney.

### THE HUMAN VESTIBULAR AQUEDUCT AND LVAS - ANATOMICAL AND RADIOLOGICAL ASESSMENTS

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The human endolymphatic duct (ED) and sac (ES) runs in a bony channel named the vestibular aqueduct (VA). It extends from the internal aperture at the medial wall of the vestibule to the external aperture at the posterior surface of the petrous pyramid. The ED is a miniscule epithelial extension of the membranous labyrinth with a diameter around 0.1-0.2 mm while the ES forms a triangular dilation in the VA and dura near the sigmoid sinus. Their functional roles are still uncertain. While pathological changes of the ED and ES have been associated with Meniere's disease abnormal dilation of the VA is observed in large vestibular aqueduct syndrome (LVAS). It is associated with progressive sensorineural hearing loss and also other inner ear malformations. VA opercular size has shown a direct correlation with audiometric outcome and borderline enlarged vestibular aqueduct measurements appear to be associated with sensorineural hearing loss. Mutations of SLC26A4 gene or Pendrin, even in the heterozygous state, were associated with enlargement of the vestibular aqueduct and abnormal vestibule. Surgical obliteration of the VA was suggested to arrest hearing loss (Wilson et al. 1997). Morphological reference data and radiological assessment of the VA in LVAS is still somewhat elusive. Here, we analyzed normal size variations and morphological characteristics in 31 specimens selected for the study harvested from autopsy. 324 plastic corrosion casts belonging to the human temporal bone collection of the Uppsala University were analyzed to obtain statistics for assessing normal size variations and radiological projections.



## **GENETICS**

#### EXOME SEQUENCING DATA INVOLVE MULTIPLE GENES AND PATHWAYS IN FAMILIAL Meniere's Disease

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Meniere's Disease (MD) has a prevalence about 0.5-1/1000 individuals. Most of MD patients are considered sporadic, even if around 8 to 10% are familial cases in European descendent population. The aim of this study is to identify common genes and pathways involved in FMD by using exome sequencing data and gene networks analyses.

Five Spanish AD families, four of them with at least two patients with definite MD and a fifth family with monozygotic twins with MD, according to the diagnostic criteria of the AAO-HNS (1995), were selected for this study. After DNA isolation and exome enrichment and capture, whole-exome sequencing was performed in 21 cases and controls in a SOLiD 5500xl platform. All the mutations found in the healthy relatives were considered as private SNVs, and excluded for further analyses.

Four different strategies were designed to filter and prioritize SNVs: a) calculation of a pathogenic variant risk (PAVAR) composite score; b) Exomiser v2 software; c) VAAST annotation tool and d) a combination of VAAST and Phevor tools. Finally, a gene ontology and pathway analysis of genes harboring deleterious variants was achieved by the Ingenuity Pathway Analysis (IPA) software for each pedigree (IPA®; Ingenuity Systems, Redwood City, CA, USA). Within each family, the top 10, 20 and 50 genes containing rare variants were selected for the analyses to define candidate canonical pathways and to find out connections between genes by means of networks.

A gene list was generated including the common genes that remained in the top 10, 20 or 50 genes from each family dataset according to the four prioritizing tools. Seventeen candidate canonical pathways were obtained for familial MD. The most significant canonical pathways were: toll-like receptor signaling, NRF2-mediated oxidative stress response and aldosterone signaling in epithelial cells. When we merged all datasets, three canonical pathways were identified: Fc epsilon RI signaling, natural killer cell signaling and CCR3 signaling in eosinophils. These new findings add new evidence to genomic and proteomic studies supporting an autoimmune hypothesis for MD.

These findings suggest a critical role in inflammatory responses, including the innate immune response and allergic reactions in the pathophysiology of MD.

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#### EXTREME TINNITUS PHENOTYPE IN MENIERE'S DISEASE

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Introduction: Tinnitus is a symptom that can appear in many different etiological conditions and that varies widely in its perceptual characteristics. This clinical heterogeneity makes difficult not only to assess different treatment approaches, but also to investigate the underlying causes. So, the delineation of tinnitus subtypes has been proposed as an imperative need in tinnitus research. In this sense, Meniere's disease (MD) is a well-defined disorder that can be used as a model to study tinnitus. One step further in this strategy is to select individuals with a strong disabling tinnitus to define a homogeneous endophenotype for genetic studies. **Aims:** To analyse the clinical characteristics of extreme tinnitus phenotype (ETP) in MD patients. Patients and Methods: Patients with definite MD according to 1995 criteria of the AAO-HNS were prospectively recruited at three hospitals between December 2014 and March 2015. Pure-tone hearing thresholds from 250 to 8000 Hz were obtained and patients filled out the Tinnitus Handicap Inventory (THI), a 25-item self-report validated guestionnaire used to guantify tinnitus severity. We defined ETP as those patients with a THI score greater than 90th percentile. Acufenometry was not performed as psychoacoustic measures do not related with tinnitus distress. Clinical features were compared between patients with and without ETP. The relationships between all variables were examined by use of regression analysis. Results: A total of 134 MD patients were included (48 males, 86 females; mean age 57 ± 27 years). Mean age of onset of MD was  $47 \pm 13$  years and mean duration was  $11 \pm 9$  years. Medium THI score was  $38.40 \pm 26.63$  and THI 90th percentile was 80, thus 14 patients were classified as ETP.

We compared current age, sex, age of onset, uni/bilateral involvement, hearing stage, antecedent of headache, type of headache, existence of hypertension or history of autoimmunity between patients with and without ETP, but no differences were found. ETP was most commonly found in familial MD 6/45 (13%) vs sporadic cases 3/70 (4%), although without statistical significance [OR=1.896 (0.69-4.831), p=0.08].

THI score was related with hearing thresholds at all frequencies, with strong correlation at 500 Hz (r=0.238, p=0.003) and 4000 KHz (r=0.232, p=0.008) in the whole cohort. This effect was increased in patients without ETP at 250 Hz (r=0.262, p=0.003) and 4000 Hz (r=0.254, p=0.006). Nevertheless, patients with MD and ETP did not show correlation with hearing threshold at any frequency in the audiogram (p>0.5).

#### Conclusions:

1. THI score in ETP is not related with hearing thresholds in MD patients. 2. Extreme tinnitus phenotype seems to be more common in familial MD.





#### GENETIC ASPECTS AND CLINICAL CHARACTERISTICS OF FAMILIAL MENIERE'S DISEASE IN A SOUTH KOREAN POPULATION

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**Objectives:** This study was undertaken to investigate the prevalence, inheritance patterns, and clinical characteristics of familial Meniere's Disease (MD) in a South Korean population.

Methods: Direct and telephone interviews were performed for 286 definite MD patients and their family members who were suspected of having MD. The diagnosis of MD in family members was made by obtaining a detailed history, performing basic neurotological examinations and reviewing hearing test results. The clinical characteristics as well as the prevalence and inheritance patterns of familial MD were analyzed.

Results: The prevalence of familial Meniere-like syndrome (at least one family member with definite MD and other members with probable MD) and definite familial MD (two or more family members with definite Meniere's Disease) were 9.8% and 6.3%, respectively, and the most common inheritance pattern was autosomal dominant with incomplete penetrance. The significant clinical characteristics of familial cases were an early disease onset and a higher prevalence of migraines.

**Conclusions:** This is the first report describing the genetic aspects of MD in a single large Asian population. The prevalence of definite familial MD was 6.3% with an incomplete autosomal dominant inheritance pattern in most cases. Early-onset age and a high prevalence of migraines were significant clinical features of familial MD in this South Korean population. These data could provide a basis for the analysis of the genetic mechanism of familial MD in Asian populations.

### IDENTIFICATION AND FUNCTIONAL ANALYSIS OF THAP1 GENE SEGREGATING VESTIBULAR PHENOTYPE IN MONOGYZOTIC TWINS WITH MENIERE'S DISEASE

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Familial Meniere's Disease has a prevalence of 8-10% of familial cases. We have performed whole-exome sequencing (WES) analysis in a family with two monozygotic twins affected by MD.

The age of onset was 38 years in both patients and the follow-up is 13 years. Both patients presented episodic vestibular symptoms, including vertigo and Tumarkin crises; both showed sensorineural hearing loss (SNHL) in the left ear and ipsilateral vestibular hypofunction, but one of them has developed a low tone SNHL in the right ear and he has a bilateral diachronic MD.

DNA was enriched for coding regions using All Exon 50MB capture kit (Agilent) and sequenced in SOLiD 5500xl platform. the After data processing, we obtained ~50.000 single nucleotide variants (SNVs) and indels per exome. We filtered the variants by in-house controls and the exome dbSNP 138 database. To prioritize pathogenic variants we annotated a score according to: a) the effect in protein structure and phylogenetic conservation by using a seven points scoring system (SIFT (Sort Intolerant from Tolerant), PolyPhen2 (Polymorphism Phenotyping v2), Graham's Matrix, GERP+ (Genomic Evolutionary Rate Profiling), Mutation taster, PhastCons and PhyloP); b) cross species phenotype comparison according to the inheritance pattern and mouse as model organism phenotype by the Exomizer software [3]; c) minor allelic frequency (MAF) <0.01.

Five SNVs remained after prioritization and filtering. Four of them, were discarded because of its low level of expression in the inner ear and by their biological function. The candidate gene THAP1 is associated with type 6 dystonia, and encodes a THAP domaincontaining protein involved in endothelial cell proliferation and proapoptotic processes. THAP1 protein is considered a transcription factor regulating apoptosis. It has normal level of expression in the inner ear and mutations in this gene cause loss of DNA binding and transcriptional dysregulation of downstream targets.

The functional impact of this novel variant is being analysed by target mutagenesis of THAP1 and cellular transfections in Jurkat cells to overexpress the gene and induce apoptosis. The effect of wild-type and mutant THAP1 genes was evaluated by using an anexxin VII apoptotic assay.

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## **GENTAMYCIN**

#### INTRATYMPANIC GENTAMICIN IN A GRADE 1 VESTIBULAR SCHWANNOMA

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The effectiveness of intratympanic administration of gentamicin (ITG) is well-known in patients with intractable Meniere's Disease. Its toxicity to the labyrinth leads to vestibular hypofunction or areflexia, which results in symptomatic control of vertigo spells and drop attacks. In 1996, Brantberg reported the use of ITG in an elderly patient with a grade 2 vestibular schwannoma (VS) who refused microsurgical tumor resection. In 2007, Mans Magnusson suggested the use of preoperative vestibular ablation with ITG and vestibular 'prehab' to enhance postoperative recovery in VS cases without preoperative vestibular areflexia (irrespective of preoperative vertigo). This treatment results in vestibular compensation before surgery and no patient complaining of vertigo after surgery.

In 2013, Gianuzzi et al. reported their experience with ITG in 4 elderly patients with small non-growing VS but incapacitating vertigo. In all 4 cases incapacitating vertigo disappeared, but 1 patient experienced persisting unsteadiness. The rationale of ITG in this population is to accelerate the progressive decline of labyrinthine function secondary to the VS. Since these (ancient) VS are not growing and on a wait-and-scan policy, vertigo symptoms are not expected to be caused by progressive decline of retrolabyrinthine vestibular nerve function. However, ephaptic stimulation of axons is still possible. The aim of the present study is to report our experience with ITG in a grade 1 VS patient with incapacitating vertigo. A 54-year-old male patient reported to our tertiary referral neurotology clinic because of incapacitating vertigo spells and instability. Video-oculoscopy examination could reveal a positional nystagmus in left-sided roll-test and right-sided Dix-Hallpike manoeuvre. Audiometry demonstrated bilateral normal hearing. Electronystagmography demonstrated a left-sided vestibular hypofunction. The total score of the Dizziness Handicap Inventory (DHI) at baseline was 70. An MRI revealed a small VS of 1 cm in the cerebellopontine angle.

A wait-and-scan policy was advised and no growth could be observed at 6-month follow-up. Because of persisting vertigo ITG was performed. Hearing temporarily worsened from an 0.5-1-2 kHz pure-tone average of 27 dBHL to 38 dBHL and recovered to 27 dBHL. The patient reported subjective improvement but symptoms recurred after 2 months. Microsurgical resection was advised by means of the retrosigmoid approach to enable hearing preservation. The posterior wall of the internal auditory canal was drilled to expose the fundus, total resection was performed while sparing the facial and cochlear nerve anatomically. The patient had an uneventful inpatient stay: facial function was normal (House-Brackmann grade I), no vertigo was experienced, hearing was functionally preserved (pure-tone average of 48 dBHL). The total score of the DHI improved 1 week after surgery to 50. A gradual improvement of instability was reported by the patient.

In VS patients with vertigo, ITG can be offered to reduce symptoms, but peripheral stimulation remains possible because of incomplete deafferentiation. Moreover, afferent signalling due to ephaptic axonal stimulation by the vestibular nerve is not affected at all by this treatment. Microsurgical resection, which inevitably results in vestibular nerve section, remains a more effective treatment if vertigo is caused directly or indirectly by the VS.



#### LONG-TERM HEARING OUTCOME AFTER INTRATYMPANIC GENTAMICIN INSTILLATION FOR MENIERE'S DISEASE

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In 1957, Schuknecht reported the first case with successful chemical vestibular ablation therapy in the management of Meniere's Disease by administering streptomycin into the middle ear. Over the years, intratympanic gentamicin (ITG) has been increasingly used because of its preferentially vestibulotoxic effect. However its application can result in iatrogenic sensorineural hearing loss as well. The aim of this study was to investigate hearing outcome after ITG application.

The ITG protocol in our hospital involves 1-hour round window application of 40 mg/ml gentamicin solution through tympanostomy. This procedure is performed under general anesthesia. We performed a retrospective study on 81 ITG cases for unilateral Meniere's Disease because of intractable vertigo spells despite optimal medical treatment. Available pure-tone audiometric data were grouped by follow-up periods: baseline before ITG, week 0-2 (N=39), week 3-4 (N=27), month 2 (N=30), month 3-4-5 (N=51), month 6-12 (N=64), year 2 (N=60), year 3 (N=30), year 4 (N=22), year 5 and later (N=28). Mean threshold levels at these follow-up periods were compared with mean threshold levels before treatment at each frequency (paired t tests). Pure-tone average (PTA) was calculated as the mean threshold at 500, 1000, 2000 and 3000 Hz. Long-term (>2 years) hearing outcome was evaluated based on the classification proposed by the American Academy of Otolaryngology-Head and Neck Surgery in 1995. Hearing improved if PTA decreased by 10 dBHL or more; hearing was considered worse if PTA increased by 10 dBHL or more. Comparison of numbers of patients in different hearing outcome groups was performed (Pearson Chi-square test).

Mean age was 54  $\pm$  13 years. Mean follow-up time was 53  $\pm$  78 weeks. PTA (mean  $\pm$  SD) before treatment was 58  $\pm$  17 dB. PTA at week 1-2 was 61  $\pm$  22 dB, which was significantly higher than before treatment (p = 0,047). For all other follow-up periods, there was no statistically significant difference (SSD) in PTA. Mean hearing threshold at 8000 Hz before treatment was 69  $\pm$  18 dB. A statistically significant difference was found for mean hearing threshold at 8000 Hz at week 1-2 (77  $\pm$  12 dB; p = 0), week 3-4 (77  $\pm$ 16 dB; p = 0,046), month 2 (71  $\pm$  13 dB; p=0,025), month 6-12 (73  $\pm$  19 dB; p = 0,032) and year 3 (81  $\pm$  18 dB; p = 0,011). Concerning long-term audiometric follow-up, hearing outcome was worse in 11 (37%), unchanged in 9 (30%) and improved in 10 (33%) cases during 3th year after treatment. During 4th year after treatment, hearing was worse in 8 (36%), unchanged in 8 (36%) and improved in 6 (28%) cases. During 5th year or later, hearing was worse in 5 (18%), unchanged in 15 (54%) and improved in 8 (29%) cases. There was no SSD between hearing outcome and long-term follow-up time.

Intratympanic application of 40 mg/ml gentamicin during 1 hour can result in significant PTA hearing loss during the first 2 weeks after treatment. High-frequency 8000 Hz is most prone to gentamicin-induced cochleotoxicity. Long-term PTA deterioration is not notably higher than the natural course of Meniere's Disease and presbyacousis. These hearing results are in accordance with previous reports. Overall, our treatment protocol has a low risk of hearing loss. However, the decision to proceed to ITG remains preferably reserved for patients with yet moderate to severe hearing loss (Meniere's Disease stage III and IV).

### SEMICIRCULAR CANALS' FUNCTION IN PATIENTS WITH MENIERE'S DISEASE TREATED WITH LOW - DOSE INTRATYMPANIC **GENTAMICIN**

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Introduction: Intratympanic gentamicin treatment is an evidence-based therapeutic option for recurrent vertigo attacks in Meniere's Disease. Either a partial deficit or a complete loss of vestibular receptor function may occur causing varying degrees of severity of imbalance and oscillopsia as well as control of vertigo. In this context the objective and quantitative assessment of the semicircular canals functions, including vertical ones seems to be valuable. **Objectives:** The objective of our study was to determine the deficits of horizontal and vertical semicircular canals after intratympanic low-dose gentamicin treatment for Meniere's Disease using video head impuls test. Methods: We conducted a prospective study of 15 subjects with unilateral Meniere's Disease treated with intratympanic gentamicin injection using low-dose protocol (concentrations of 20 mg/ml, 1-2 injections, waiting a month between injections) and followed all subjects for 1.5 year. We measured the gain of the angular vestibulo-ocular reflex in each of the canal planes before, 4-6 and 12-18 months after treatment with intratympanic gentamicin by using video head impulse test, additionally low frequency changes of horizontal vestibulo-ocular reflex were monitored using the bithermal caloric irrigation. Results: Before treatment 10 patients presented VOR gain of all semicircular canals in the normal range on the affected side (0.92 +/- 0.20, 0.83 +/- 0.30 and 0.79 +/- 0.25 for the horizontal, anterior and posterior canal respectively). The remaining 5 subjects had decreased gain of horizontal and/or posterior canal (0.67+/- 0.13, 0.63+/- 0.15). After gentamicin administration the vestibuleocular gain measured 4-6 months after treatment was significantly reduced in 4 subjects in each canal on the treated side (0.33 +/- 0.12, 0.35 +/- 0.15, 0.31 +/- 0.17 for the horizontal, anterior and posterior canal respectively), while 3 of these subjects had normal gain in each canal before treatment. In 11 subjects gentamicin administration resulted in a moderate decrease in gain of horizontal canals but in 5 of them did not cause a significant reduction in gain of vertical canals: both in anterior and posterior or only in anterior. Measurements made during 12-18 months after gentamicin administration showed a return to normal gain value in single canals in 4 patients. Abnormal caloric asymmetries between normal and affected side (averaged 47% +/- 33%) were found in 10 subjects before treatment and deteriorated to 69% +/- 31 % when measured 4-6 weeks after treatment. No significant changes in caloric asymmetries were found in tests performed after 12-18 months. Conclusions: Our results suggest that vertical canals are less affected then horizontal ones and partial restoration of the semicircular canal function is possible in intratympanic low-dose gentamicin.



## **HEARING AIDS**

#### QUALITY OF LIFE BEFORE AND AFTER HEARING AIDS

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Introduction: Hearing loss is the 3rd most prevalent chronic condition in older adults. It has a far reaching effect on the physical, mental and vocational aspects of life of an untreated individual. This is the first study locally, which allows us to ascertain the impact of hearing loss on quality of life.

**Objectives:** This study aims to achieve the following: 1. Determine the quality of life (QOL) before and after hearing aid intervention. 2. Ascertain any significant factors that affect QOL after hearing aid intervention 3. Evaluate for any difference in QOL between unilateral versus bilateral hearing aids use. 4. Determine the compliance to hearing aid use and reasons for non-compliance.

Methods: Patient with untreated hearing loss, above 21 years of age inclusive, were approached by the attending audiologist in a sequential manner. Face to face interview were conducted based on HHIE (Hearing Handicap Inventory for Elderly) for patients above 65 year of age and inclusive and HHIA (Hearing handicap Inventory for Adult) for patients before 65 years of age. The questionnaires were administered again on follow up in 3 months. The average hearing loss of the better hearing ear was used for analysis. The severity of hearing loss was classified using American Speech Language Hearing Association classification of hearing loss. Defaulters were contacted via phone and their reasons for dropout/non-compliance recorded.

Results: Total of 63 patients were recruited over 3 months duration. This comprised of 29 males and 32 females with mean age of 70 years ± 10 years. Significant improvement in QOL scores were evident after hearing aid intervention with average scores of  $25.13\pm24.74$  prior to intervention and  $7.13\pm12.44$  post intervention (p<0.001). Patients who are widowed have 40% (p=0.016, 95%CI: 8.0%, 72.1%) lower in percentage change in QOL post fitting compared to patients who are single. The benefit of hearing aids is independent from the degree of hearing impairment (p=0.4358). Eighty-two per cent are compliant to the use of hearing aids. Malays have 98% (p=0.003, 95% CI:76%, 100%) lower odds of compliance compared with Chinese. Severity of hearing loss does not significantly impact on the compliance (p=0.2998). Reasons for non-compliance include cosmesis, discomfort and occlusal effect. Bilateral hearing aids do not confer any additional improvement in QOL scores compared to unilateral aid in our study (p=0.2497). Conclusion: Unaided hearing disability is more pronounced in groups with more severe hearing loss while benefit of hearing aids is independent from the severity of hearing impairment. Social support eq marital status does impact on the improvement in QOL post fitting. Lower compliance rate in certain ethnic group could be related to cultural perception of hearing aids. Hearing rehabilitation with hearing aids results in significant improvement in QOL and should be advocated.

## **IMAGING**

COST EFFECTIVENESS OF USING CONTRAST-ENHANCED MAGNETIC RESONANCE IMAGING FOR SCREENING UNILATERAL **HEARING LOSS** 

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The purpose of the study is to calculate the cost of contrast material used for enhancement in MRI for screening unilateral hearing loss. The patients attended our department between 2007 and 2014 were evaluated. 695 patients had contrast-enhanced MRI for unilateral hearing loss. The 24 of them were diagnosed as having acoustic neuroma. All sequences were evaluated again by the same radiologist. The determining power of the pulse sequences and the cost difference were calculated. Only very small acoustic neuromas need contrast enhancement for differentiating from the artifacts.

### HIGH SIGNAL ON 3D FLAIR. A PREDICTABLE FACTOR FOR PROGRESSION TO MENIERE'S DISEASE IN SUDDEN HEARING LOSS

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**Objective:** Three-dimensional fluid-attenuated inversion recovery (3D-FLAIR) image in MRI has recently been developed to detect high concentrations of protein or hemorrhage. Other articles have previously reported that 50% of patients with sudden hearing loss show high signals in the affected inner ear on 3D-FLAIR MRI. However, the relationship between 3D-FLAIR findings and hearing prognosis is unclear. The aim of study was to evaluate the relationship between the results of 3D-FLAIR MRI and prognosis (especially progression to Meniere's Disease) in sudden hearing loss.

Materials and Methods: Retrospective chart review of a clinical data from August 2011 to December 2014, 450 patients diagnosed as unilateral sudden hearing loss and performed temporal bone MR within 2weeks from the onset of hearing loss. Hearing loss type was divided to 4 group: Low tone loss, high tone loss, flat, profound. The low-tone loss type meets the following criteria: the average hearing level at 250, 500 and 1 kHz is at least 10 dB worse than that at 2, 4, and 8 kHz. 8 patients were categorized as low tone loss. Profound type was defined as the average hearing level at 500Hz, 1kHz and 2kHx was worse than 90dB. Whirling type vertigo was checked by chart reviewed. Meniere's Disease was evaluated according to the 1995 AAO-HNS criteria. And high signal intensity on FLAIR image was checked by radiologist.

Result: Among the 450 patients, high signal intensity on 3D-FLAIR image was observed in 75 patients. Age, sex, affected ear was no difference between high signal group and no signal group. In audiogram, high signal group showed worse result. (p=0.047) But final audiogram and recovery was no statistical difference. High signal intensity was more frequently observed in profound hearing loss. (p=0.000) In cases of High signal on FLAIR image, the more patients had experienced vertigo attack. (p=0.010) And high incidence of positive on FLAIR image was observed in Meniere group. (p=0.026) Conclusion: If a patient had high signal intensity on FLAIR, it tend to have worse hearing and the likelihood of vertigo attack could increase. In cases of High signal on FLAIR image, the more patients had experienced vertigo attack and had tendency of high incidence on patients of Meniere's Disease. Positive findings on FLAIR image might be considered as predictable factor for Meniere's Disease in sudden hearing loss patients.

### IMMUNE-MEDIATED DISEASE

#### MICROGLIA IN MENIERE'S SYNDROME

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The etiology of Meniere's syndrome remains unknown. An immune-mediated etiology is supported by several lines of evidence including: 1. elevated levels of antiviral immnoglobulins in endolymph, 2. identification of viral particles in vestibular ganglion cells 3. increased values of circulating immune complexes in patients with Meniere's syndrome and 4. the favorable clinical response observed in some patients with the administration of steroids and or antiviral therapy. Our lab has recently identified a vast array of microglia-like cells in the human inner ear. Using immunohistochemistry, we describe the distribution and activation state of microglia-like cells in documented cases of definite Meniere's syndrome in human temporal bone specimens with histories of active and inactive disease at the time of death. Age-matched controls and cases of prior viral labyrinthitis were also examined. In each condition we correlate the distribution and activation of microglia-like cells to the clinical history.





#### UNILATERAL NEUROSENSORIAL HEARING LOSS AND MULTIPLE SCLEROSIS

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Aim: Discover and recognize from a case report one strong point between ENT and neurology: unilateral sensorineural hearing loss and multiple sclerosis

2. evaluate the role of a MRI examination in discovering this strong conjunction

3. nevertheless underestimate a unilateral hearing loss in a young person, always perform a MRI to get a firmer diagnose J.R, female, 21 years old comes to our clinic complaining of a grave unilateral hearing loss from her right ear from one month and a half. After a normal otoscopy we performed an audiometry showing a severe unilateral neurosensorial hearing loss Au dx, her left ear normal, timpanometry normal. Than from a consult with the neurologist we did not discover any neurologic sign, her neurologic tests were normal. We performed an MRI and the radiologist found a periventricular left lesion of the white substance. For the hearing loss although afterwards one month and a half-hour I gave her vasodilatators, corticosteroids and vitamino therapy for a month but I found a very little improvement. After one month when she came back she had also began to have a motor difficulty in the extremities and sometimes a robotic speech when talking. She also has began taking the therapy for multiple sclerosis.

Conclusion: It is very rare but one of the clinical signs discovering the MS is a sudden grave unilateral neurosensorial hearing loss in a young patient and we discovered it from a good consult with the neurologist and of course with the goal standard examination: MRI of the head.

#### UNILATERAL SENSORINEURAL HEARING LOSS AS IMMUNE-MEDIATED INNER EAR DISEASE

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**Objective:** The aim of the present study was to show that the positivity of aspecific immunological tests could be found not only in bilateral AIED but also in sudden and progressive unilateral SNHL. Methods: To this purpose, the positivity of non-specific immunological tests was assessed in patients who came to the observation for progressive or sudden, bilateral or unilateral sensorineural hearing loss. Patients suffering from unilateral sensorineural hearing loss (SNLH), sudden or bilateral progressive symmetric or asymmetric SNHL All the patients underwent a battery of blood exams to evaluate the immunological response, consisting in ANA, ENA screening, anti-thyroperoxidase (anti-TPO), anti-thyroglobulin and antibody against smooth muscle (ASMA). The patients were clinically divided into two groups: the first one, Group A (39 patients), were affected by bilateral hearing loss and the other one, Group B (33 patients), was formed by patients presenting with unilateral hearing loss.

Results: Overall, in both groups a significant positivity of nearly 70% of aspecific immunological test has been shown. The most frequently positive antibodies were ASMA and ANA in both groups, without statistical differences. Considering the correlation between positivity/negativity and systemic autoimmune pathologies, in the positive Group B a high incidence of thyroid pathologies has been found and in positive Group A a high percentage of systemic autoimmune diseases, not comparable with the values reported in general population.

Conclusions: The authors suggest to add to the clinical suspicion of autoimmune inner ear syndrome the possibility and probability o an AIED aetiology also in monolateral SNHL, mostly in the progressive tipology.

## **INNER EAR FLUIDS DYNAMICS**

#### ADRENERGIC STIMULATION-MEDIATED TRANSEPITHELIAL CURRENT FROM HUMAN ENDOLYMPHATIC SAC EPITHELIUM

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**Objective:** This study was performed to investigate the modulation of transepithelial current from human endolymphatic sac (ES) epithelium by adrenergic and cholinergic stimulation and the difference of the ion channel activity modulated by adrenergic and cholinergic stimulation between healthy subjects and Meniere's Disease patients. Methods: Normal human ESs were harvested during acoustic tumor surgery using the translabyrinthine approach. The ESs of Meniere's Disease patients was obtained during ES decompression. The luminal side of ES was exposed and folded for transpithelial current measurement. The vibrating-probe technique was used to measure transepithelial currents of apical side of ES. Specific ion-dependent current under adrenergic and cholinergic stimulation was measured using electrophysiological and pharmacological methods. Adrenergic and cholinergic stimulators [isoproterenol (10  $\mu$ M)and epinephrine (100  $\mu$ M) for adrenergic stimulation; substance P (10 µM), carbachol(10 µM) for cholinergic stimulation) were used for evaluation of each response. Specific ion channel blockers for Na+ channels, K+ channels, CI- channels were applied for identification of ion channels dependent on adrenergic or cholinergic stimulation. The adrenergic receptor antagonists ICI-118551 and CGP-20712A (specific antagonists of  $\beta$ 1- or  $\beta$ 2adrenergic receptors, respectively) were applied for identification of subtype of adrenergic receptor. **Results:** Changes of transepithelial current by adrenergic stimulation in human ES epithelium were various. Adrenergic stimulation induced cation absorption/anion secretion current or cation secretion/anion absorption current depending on the area of ES. The isoproterenol-dependent cation absorption current, cation secretion current, and anion secretion current was blocked by bumetanide  $(10 \,\mu$ M), Ba2+  $(1 \,m$ M), and DIDS  $(10 \,\mu$ M)in normal human ESs, respectively. There was no effect of adrenergic stimulation (isoproterenol and epinephrine) in ESs of Meniere's Disease patients.

Conclusions: These results suggest that transepithelial current from human ES epithelium was modulated by adrenergic stimulation and cholinergic stimulations. The involved ion channels and transporters for each stimulation are NKCC, K+ channels and CI- channels. However, transpotchelial current in the ES of Meniere's Disease patients was not likely to be changed by adrenergic stimulation. These results reflect that excessive stress-mediated adrenergic or cholinergic stimulation in the inner ear can influence on the ion channel functions of inner ear epithelium, which can aggravate the symptoms of Meniere's Disease by disturbing inner ear homeostasis.





#### BAROTRAUMATIC PERILYMPHATIC FISTULA: PROPOSED APPROACH TO DIAGNOSIS AND MANAGEMENT

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Objectives: The diagnosis of barotraumatic perilymph fistula (PLF) is controversial due to the variability in patient presentation and difficulty in pre-operative evaluation. Symptoms like hearing loss, ear fullness and dizziness can develop following minor barotrauma such as Valsalva, nose blowing and straining. The aims of this study are to present the clinical manifestations of barotraumatic PLF for providing appropriate diagnosis and management.

Methods: We reviewed medical records of the patients who underwent surgical exploration under the impression of barotraumatic PLF. 19 patients were enrolled and the causes, symptom and signs, and operative findings and outcomes were analyzed.

Results: Among the 19 patients, 9 patients were classified as the external trauma (car accident, slap injury) and 10 patients had internal trauma (lifting, nasal blowing, straining, etc). RW fistula was mainly observed in internal type(5 cases among 8 RW fistula) while every OW cases were caused by external type(4 cases of OW fistula). Most symptoms are present in serial order regardless of origin. However dizziness tends to come first in OW and hearing loss usually preceded in RW. Total six patients had positional nystagmus and all of them had hearing loss before dizziness. They had RW fistula(n=3) except the cases with unknown origin(n=3). The character of nystagmus was ampullofugal nystagmus which is different from typical BPPV(benign paroxysmal positional vertigo). It usually involved bilaterally and lacks fatigability and reversibility with longer duration. Hearing outcome was better after early exploration. When we compared the hearing outcome according to the frequency, and hearing gain was smaller in high frequency. Conclusions: The clinical presentation of barotraumatic perilymph fistula could be variable depending on location of fistula (OW or RW) and degree of damage. Fistula mainly occurred in RW in the internal type while OW fistula was only found in the external type. Regarding fistula site, dizziness comes first when it occurs in OW and hearing loss is preceded when it occurs in RW. Because RW fistula can induce positional nystagmus, it is important to differentiate from BPPV. What's different from typical BPPV is that PLF doesn't show reversibility or fatigability and it has longer duration. It forms an ampullofugal flow within the semicircular canal. In addition, early surgical intervention in clinically suspected PLF seems to be very essential for improvement of symptoms.

#### THE INNER EAR-A NOVEL TARGET FOR INSULIN ACTION AND RESISTANCE-IMPLICATIONS FOR DIABETES

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Background: A number of studies have demonstrated an association between diabetes and inner ear morphological as well as functional alterations as well as an association between dysregulated vasopressin/cAMP signaling and Menieres disease. However, whether the inner ear is a direct target for insulin signaling and/or insulin resistance or whether insulin can impact on cAMP signaling in the inner ear is not known.

In two previous studies we have started to map insulin- and cAMP signaling networks in human inner ear; for example, the insulin receptor, the insulin receptor substrate 1, the insulin sensitive glucose transporter 4 and several cAMP degrading enzymes (PDEs) were shown to be expressed in the sensory epithelium of the human saccule. In on-going studies we continue the mapping work and we have also started to investigate the functional role for selected insulin/cAMP signaling proteins in vivo using MR in combination with gadolinium as read-out for endolymphatic hydrops (EH).

Method: Human saccules used for IHC are obtained during the removal of vestibular schwannoma. A model for functional studies of identified target proteins has recently been set up and involves the treatment of CBA/J or C57BL6 mice with continuous administration of vasopressin via osmotic pumps using MR in combination with gadolinium as read-out for inner ear fluid homeostasis. **Results:** IHC staining demonstrates the expression of PDE3B-a membrane associated target protein for insulin action in energy storing cells-in the apical part of the human saccule sensory epithelium. PDE4D was shown to be expressed in the hair cells of the sensory epithelium together with aquaporin 2. Interestingly, others have shown a functional interaction between PDE4D and aquaporin 2 in kidney cells. In addition, preliminary results show the expression of the IGF1 receptor and the insulin target NaK-ATPase in supporting cells and the kinase mTOR and the exocytotic protein SYT7 in hair cells. Administration of vasopressin to was shown to induce EH in mice as shown by MR. In on-going studies we have started to test the ability of inhibitors for PDE3 and PDE4 to influence vasopressin-induced EH. To this end, the results indicate that PDE3 inhibition potentiates vasopressin induced EH indicating an important role for this enzyme in the regulation of fluid homeostasis. Significance: Although the integrated insulin/cAMP networks are well established regulators of energy metabolism, in the inner ear other processes related to water and ionic homeostasis could be targeted as well. For example the NaK-ATPase is known to be regulated by insulin in kidney cells. Thus, the ongoing studies aiming at evaluating the role for insulin signaling/action in the inner ear and the role of cross-talk between insulin and cAMP systems for example via PDEs will contribute with new knowledge on the regulation of inner ear functions and generate new strategies for prevention and treatment of inner ear disorders.

## MEDICAL TREATMENT

#### OPTIMAL MANAGEMENT OF MENIERE'S DISEASE

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Several treatment options have been introduced to control Meniere's Disease (MD). There is currently no gold standard treatment for MD. The purpose of this study was to analyze the clinical course and treatment flow in patients with MD A retrospective study was performed on 168 patients who were diagnosed as definite MD from May 2010 to May 2014 and were followed up at least 1 year. The authors investigated the course of disease and the results in our patients according to the treatment options. Several clinical parameters including frequency of vertigo, audiometry, caloric and rotation test were reviewed and analyzed according to the guideline of the AAO-HNS (1995), if necessary. Among 168 patients, vertigo was resolved or improved in 149 patients (88.6%) with medical management. Three patients needed further treatment (endolymphatic sac decompression: 3, ITGM: 7 ITSI : 9). Among 7 patients who got ITGM, 6 patients were followed up for more than 1 year after injection. Five patients (83.3%) showed successful control of vertigo.. Vertigo was controlled by supportive treatments or medication in 88% of definite MD patients. And ITGM could effectively control vertigo for intractable MD patients.



7<sup>th</sup> International Meniere's Disease Inner Ear Disorder



#### TREATMENT OF PERIPHERAL VESTIBULAR VERTIGO

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Vertigo is one of the most frequent symptoms encountered in medical practice. Among the reasons for resorting to the doctors of different specialties dizziness is 3-4%. About a third of patients seeking to ENT doctors, mark the different types of dizziness.

Aims and objectives: To evaluate the efficacy and tolerability of Arlevert use as monotherapy for the treatment of symptoms of peripheral vestibular vertigo. The main interest position - change the severity of symptoms of peripheral vestibular vertigo and autonomic disorders.

Methods. The study included 20 patients with peripheral vertigo in age from 20 to 70 years. The average age of the subjects was 53,3  $\pm$  13,9 years. Inclusion criteria in the study were patients with symptoms of peripheral vertigo over 18 years, as well as obtaining informed consent. Contraindications to using Arlevert, mental disorders, affecting an objective assessment of the patient's condition, benign paroxysmal positional vertigo were exclusion criteria of the study. Patients taking the drug 1 tablet 3 times a day. Efficiency Arlevert assessed by the dynamics of indicators of severity and intensity of vertigo symptoms of autonomic VAS (visual analogue scale). The survey was conducted prior to the appointment of the drug, as well as 7 and 28 days of therapy.

Results. In the primary treatment for the severity of vertigo VAS averaged 2,2 + 0,9 points. On the 7th day of therapy on the severity of vertigo VAS averaged 0.3  $\pm$  0.5. On day 28 the severity of vertigo VAS averaged 0.1  $\pm$  0.2 points. Thus there was a significant reduction in the severity of vertigo (P < 0,001).

Intensity of vegetative symptoms of VAS was the primary treatment averaged  $1,3 \pm 1,2$  points. On day 7 of therapy on the severity of symptoms of autonomic VAS averaged 0.3 + 0.6 points. On day 28 the severity of symptoms of autonomic VAS averaged 0.1 + 0.2points. Thus there was a significant reduction in the severity of autonomic symptoms (P <0,001).

In general, the drug was well tolerated, during treatment in 3 (15%) patients reported somnolence. This effect was observed during the first week of treatment. Starting from the second week of the drug in patients was observed drowsiness. Thus, all patients completed the study. The incidence of premature discontinuation of treatment was not. Efficacy evaluated as "excellent" in 19 (95%) subjects, as "good" - in 1 (5%). Portability rated as "excellent" in 17 (85%) subjects, as "good" in 3 (15%).

Conclusions. Our experience in treatment of peripheral vestibular vertigo drug "Arlevert" showed it sufficient clinical efficacy and tolerability. Thus, the drug "Arlevert" is effective in treating symptoms of peripheral vestibular vertigo.

## OTOTOXICITY

### PLATINUM-INDUCED OTOTOXICITY IN CHILDREN: COMPARISON OF DIFFERENT OTOTOXICITY CLASSIFICATION

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Introduction: Cisplatin and carboplatin are important antineoplastic agents which are used for treatment of various paediatric malignancies. Unfortunately some side effects like ototoxicity and nephrotoxicity hinders their usage of higher doses. Hearing loss related to these agents is irreversible and occurs at cumulative doses. Moreover these children who have been exposed to higher doses can be candidate for cochlear implantation. The first classification to describe ototoxicity was Brock's classification. Other ototoxicity classifications have been established to overcome some weak points of Brock's classification afterwards. Aim: To evaluate frequency and intensity of hearing impairment in children who received cisplatin/carboplatin treatment according to six different ototoxicity classifications and to audiologically examine these 6 different ototoxicity classification and to discuss their suitability.

Material Methods: Data of 87 children who received cisplatin/carboplatin therapy were respectively analysed. All patients were evaluated by otoscopic examination, pure tone audiometry, otoacoustic emission and acoustic immitansmeter before and after treatment. Ototoxicity seen in these patients was evaluated by NCI, Brock, Muenster, ASHA, Chang, and SIOP Boston classifications. Results: The mean age was 11,2 (3-17 years) years old. Ototoxicity was observed in 33, 31, 35, 34, 30 and 33 patients according to following NCI, Brock, Muenster, ASHA, Chang and SIOP Boston classifications respectively. Consistency of these classifications was analyzed by intraclass correlation test and it was found that these tests were highly consistent with each other (ICC: 0,834). **Conclusion:** While treating pediatric oncology patients toxicity related to therapy and life quality are important factors to not underestimate. For this purpose various ototoxicity classifications has been described. It seems that all these classification were in high consistencies with each other.

#### OTOTOXICITY OF PARENTERALY ADMINISTRED GENTAMYCIN- CASE REPORT

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Aim: To present a case report of bilateral sensorineural hearing lost after parenterally administered Gentamycin as a therapy for acute Bronchopneumonia

Method: Case report of 36 years old woman which has been treated parenterally with Gentamycin twice a day in dose120 mg ( 240 mg daily) for a period of 12 days, as a therapy for acute Bronchopneumonia at Clinic for infectious diseases. At first 6 days of hospitalization she was high febrile (39,5-40,5 C body temperature). After 3 days of therapy she had felt bilateral hearing lost and tinnitus, and the therapy was still the same in the following 10 days, without ORL examination and without audiology testing. After 2 months the patient had first ORL examination and audiology testing was provided - Tonal liminar audiometry, tympanometry, OAE - Dp OAE, Evoked potentials.

Results: TLA showed bilateral sensorineural hearing lost with slope configuration of Audiogram (in range 125Hz-8 kHz), bilateral hearing lost of 68 %, tympanometry bilaterally normal result type A, Dp OAE with bilateral hearing impairment, EP with normal configuration. The patient was treated with high dose vitamin therapy, vasodilatation drugs in a period of a 2 months without any hearing improvement.

Hearing aids were provided.

**Conclusion:** Aminoglycoside antibiotics such as Gentamycin should not be included in treatment of acute infectious diseases because of its ototoxicity. High percentage of bilateral hearing lost, tinnitus and quality of life impairment are very high price for treatment with ototoxic drugs.





## **PRESSURE TREATMENT**

#### EFFECT OF TRANSTYMPANIC VENTILATION TUBE INSERTION IN INTRACTABLE MENIERE'S DISEASE

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**Objectives:** Transtympanic ventilation tube as a treatment option for Meniere's Disease has been reported, but the results have been controversial. As a treatment for patients with intractable Meniere's Disease, insertion of a ventilation tube into the tympanic membrane was carried out, and the effect of therapy was analyzed.

Methods: Five patients (2 males, 3 females; age range, 51-79 years) with active Meniere's Disease received ventilating tubes in the affected ear and postoperative changes in symptoms (i.e., incapacitating vertigo and hearing loss) were investigated. The efficacy of treatment on vertigo attacks and hearing loss with this disease was evaluated according to AAO-HNS (1985) criteria.

Results: At 42 months of treatment, one of the 5 patients showed complete control of vertigo, two achieved substantial control and two achieved insignificant control. On the other hand, hearing level was unaffected by treatment.

**Conclusions:** This treatment might have short-term effects in reducing persistent vertigo in some patients with Meniere's Disease, and so might offer an additional treatment option because of the simple, less-invasive procedure.

## **STEROID TREATMENT**

#### EVALUATING EFFECTIVENESS OF INTRA-TYMPANIC DEXAMETHASONE INJECTION OF MENIERE PATIENTS WITH ALTERATION OF ELECTROCOCHLEOGRAPHY

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Meniere's Disease is a chronic disorder of inner ear . . Mechanism of disease is incomplete resorption of endolymphatic fluid. Cochlea especially Scala media is the most common site of involvement. ECOGis non- invasive method for records of cochlear action potentials. and applied to diagnosis of this disease. The use of intra-tympanic dexamethasone(IT-Dex) to reduce the severity of these symptoms has been gaining popularity in recent years. Corticosteroids promote blood flow of inner ear to 26%, as mentioned by some studies.

patients with alteration of electrocochleography.

whom non responder to medical treatment was selected...

every week(3 doses totally twith a week interval) was carried out. We recorded Post treatment ECOG and audiometry, one month after 3rd (IT-Dex) injection, and Evaluated clinical sign of vertigo and tinnitus 1 to 6 months after treatment. 36 patients included in this study. Mean age of patients was 39/89. 21 (58/3%) of patients was male and 15(47/3%) was female.22(61/9%) of patients had right ear and 14(38/1%) of patients had left ear involvement. Mean average time of involvement was 4/06 year. positive familial history was obtained in 7 (19/4 %) of patients. 4 (11%) patients had improvement in hearing status based on AAO-HNS criteria and others (88%) had not this. Worsening of hearing occurred in none of participants. PTA level after of injection not correlated with IT-DEX (P value=0.492) instead of SDS after of injection coordinated with IT-DEX (P value=0.008).The relationship between tinnitus and IT-DEX was not significant (P value =0.334). Evaluation of vertigo in this study based on numeric value scale of vertigo index according to AAO-HNS, relationship between vertigo before intervention and vertigo 1 month after intervention and between 1 month after intervention and 6 months later was significant (in both <0.001).

=0.2).

although this value diminished to 19.5% at the end of 6 months dramatically. Improvement in ECOG outcome was not significant before and after of intervention (P value =0.052). The results of a single trial provide limited evidence to support the effectiveness of treatment in patients with Meniere disease Also we have not control group for this research. This trial demonstrated a statistically and clinically significant improvement of the frequency and severity of vertigo measured1month after the treatment was administered. Without additional treatment this effect diminished significantly during other 6 months. Intra- tympanic Steroids can be used to short acting treatment option for treatment of vestibular symptom in Meniere disease.

ECOG not correlate with this treatment and not to be used for evaluation of this modality.

- Evaluating the effectiveness of intra-tympanic dexamethasone injection in improvement of symptoms of unilateral definite Meniere
- A before and after study including 36 adult patients of a tertiary referral ENT clinic whom definite, unilateral Meniere's patients
- Baseline ECOG and audiometry obtained, treatment started with 4mg (IT-Dex)in postero-superior guadrant of tympanic membrane
- But this relationship was not significant between vertigo before intervention and vertigo scale in 6 months later after that.(P value
- According to this study, one month after intervention, at least 75% of patients had one class improvement in their former class



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## **SUDDEN DEAFNESS**

#### PROGNOSIS OF SEVERE TO PROFOUND IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS

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While a severe to profound sudden sensorineural hearing loss (SSNHL) may cause serious disability in verbal communication, there have been little studies focusing on this high degree SSNHL. The present study was aimed to investigate the characteristics of hearing recovery in a high degree SSNHL (>70 dB). Three hundred and two SSNHL patients were enrolled. For a long-term followup, 46 patients were evaluated. Hearing level was examined by pure tone audiometry on day 1, week 3, month 3, month 6, and year 1 or after. According to the degree of the initial hearing loss, the patients were divided into 4 groups from 70 dB to  $\geq$ 100 dB. After 3 weeks, the recovery rate and mean hearing gain was 61%, 23.85dB in the 70dB group, whereas 10%, 6.61dB in the  $\geq$ 100dB group. There was a significant correlation between 3 week-recovery and final hearing outcome, indicating that an early recovery can be a prognostic factor for the final recovery in severe to profound SSNHL. Since recovery after 3 months is rare, an early hearing intervention like hearing aid or cochlear implantation should be considered in the high degree SSNHL to restore the patient's verbal communication.

#### RELATIONSHIP BETWEEN HEARING THRESHOLD AT THE AFFECTED AND UNAFFECTD EAR IN UNILATERAL MENIERE'S DISEASE

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Hearing loss in Menière's disease has been described to affect above all the low frequencies (upward curve) with a tendency to become irreversible and nonfluctuating at the higher frequencies (peaked curve) over time. The aim of the study was to determine the effects of MD on hearing function on the basis of differences existing between the affected and the unaffected ear in a group of patients affected by definite unilateral MD and whose contralateral ear was not affected by any disease other than age related hearing loss (ARHL). Following this procedure we have also evaluated the possible effects of age and disease duration on hearing loss in MD. The study group consisted of 86 subjects affected by definite unilateral MD. The second inclusion criterion was the absence of pathologies at the unaffected ear other than ARHL. In our sample hearing threshold at the affected ear is characterized by a peaked curve but detracting threshold of the normal ear the resulting curve becomes an upward sloping curve due to a higher degree of suffering at the lower frequencies. On the basis of differences existing between affected and unaffected ear our data suggest that threshold evolution is more related to disease duration rather than age.

### VESTIBULAR SCHWANNOMA IN SUDDEN SENSORINEURAL HEARING LOSS PATIENTS

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Introduction: Sudden sensorineural hearing loss (SSNHL) has several etiologies. It may be a presenting symptom of retrocochlear lesions and other CNS problems. High sensitivity and specificity rates define magnetic resonance imaging (MRI) of the brain as the gold standard for the diagnosis of retrocochlear pathologies. This study aimed to establish the incidence of CNS lesions in patients with SSNHL, and we report several unusual cases among these patients. Methods: We reviewed retrospectively the charts and MRI findings of all adult patients who presented with SSNHL between January 2012 and May 2015. We utilized gadolinium enhanced temporal bone MRI as a screening method in SSNHL patients. The study included 252 patients, 137 females and 115 males, with an average age of 51 years (range 8-82 years). Results: Of the 252 patients with SSNHL, vestibular schwannoma (VS) was found in 18 (7.1%) cases. the patients have several other CNS diseases, as Rathke's cleft cyst, meningioma, vascular anomaly, pituitary adenoma, etc. we used glucocorticoid treatment and timely and short-term medication.

SSNHL patients. Recently, as a result of the increasing widespread use of MRI, more patients with vestibular schwannoma (VS) than expected have been detected among those with SSNHL. MRI would seem to be mandatory in all cases of SSNHL.

## SURGERY

#### ENDOSCOPIC INLAY BUTTERFLY (CARTILAGE) TYMPANOPLASTY

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tympanoplasty technique was presented.

Sixteen patients (8 males, 8 females) with central tympanic membrane perforation due to chronic otitis media and no active ear infection for at least two months were included in this study. All surgical procedures were performed with the help of 0°/4 mm diameter rigid endoscope. Perforation dimensions were measured after perforation edges were refreshed. Perforation diameters ranged from 2 to 6 mm. Tragal cartilage graft was prepared like butterfly wing as in Eavey technique and it was inserted through the perforation like grommet ventilation tube. Two patients with large perforations more than two-thirds of the tympanic membrane had minimal perforations at the edge of the cartilage which was closed with fatty graft taken from ear lobe. At the end of the follow-up period, tympanic membrane perforation closure was found as (15/16) %93.7. The preop/postop difference in air-bone gap decreased from 18.5 dB to 8.25dB in average. The endoscope has advantages especially in clear vision of anterior tympanic membrane perforations. The remaining small perforations are also detected easily.

This technique can be used safely in the situations with minimal hearing loss, clear middle ear, small and medium central tympanic membrane perforations.



- Conclusion: Some vestibular schwannomas have SSNHL as initial symptoms and CNS lesions were sometimes founded incidentally in

- In this study, preoperative and postoperative anatomic and audiological results of endoscopic and inlay butterfly cartilage



#### OTONEUROLOGICAL ASSESSMENT IN LONG TERM FOLLOW UP AFTER VESTIBULAR NEURECTOMY FOR MENIERE'S DISEASE

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Background: Vestibular neurectomy is now regarded as the most effective method for treating severe cases of peripheral vestibular disease. There is a lack of data about long term instrumental results.

Aim: To investigate otoneurologic assessment in 12 patients that underwent vestibular neurectomy for Menière's disease.

Methods: The instrumental assessment consisted of visuo – ocular reflexes, caloric tests, vestibular ocular reflexes (VOR), cervical and ocular myogenic potentials and tonal and speech audiometry. Subjective status was investigated by the Dizziness Handicap Inventory (DHI). The mean time between surgery and the otoneurological assessment was 7 years (SD:3.16).

Results: All patients had good subjective outcomes as measured by DHI (mean value 32.73; SD: 24.74). Two patients (16.7%) had a spontaneous nystagmus. A mild response at the caloric test on the operated side was present in 2 patients (16.7%), with side prevalence greater than 25%. Three patients had cervical vestibular evoked myogenic potentials with low amplitudes and high thresholds. One of them belonged to those with caloric responses. Only 1 patient had weak ocular vestibular myogenic potentials on the operated side. The video head impulse test showed a gain greater than 0.5 for the posterior semicircular canal in 4 patients (33.3%), for the anterior semicircular canal in 2 patients (16.7%) and for the lateral canal in 5 patients (41.7%). In 1 patient the presence of cervical evoked myogenic potentials was associated with normal posterior semicircular canal VOR gain (0.86). This was a symptomatic patient with DHI = 74.

Conclusions: We do not have definite explanations for the presence of mild caloric responses in 2 cases and the presence of cervical and ocular myogenic potentials associated with low DHI scores; we believe that instrumental data may highlight anomalies that do not relate to subjective outcome. In contrast, the presence of cervical potentials associated with normal VOR in the posterior semicircular canal could confirm the recent hypothesis that the inferior part of vestibular fibers might merge with cochlear fibers. In conclusion even if neurectomy might not always determine complete vestibular areflexia, it surely controls symptoms in case of severe peripheral vestibular disease.

#### OUTCOME OF ATTIC RECONSTRUCTION AFTER MINIMAL INCISION ATTICOANTROSTOMY APPROACH LASER SURGERY FOR CONGENITAL CHOLESTEATOMA (MILC) - SURGICAL EXPERIENCE FROM 400 CASES

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Congenital cholesteatoma (CC) is an ossicle origin middle ear tumor that shows early ossicle destruction rather than attic destruction of acquired cholesteatoma. Atticoantrostomy approach (AA) is a useful surgical technique to visualize ossicles widely by combining otosclerosis drilling (anterior tympanotomy) and transcanal atticotomy, which provides better exposure of anterior attic and tympanic sinus compared to CWU mastoidectomy with posterior tympanotomy.

Methods. Our surgical technique is minimal incision atticoantrostomy approach Laser surgery for Congenital cholesteatoma (MILC), and we have over 400 CC cases. We reviewed the outcome of endaural AA regarding feasibility to complete CC surgery and the outcome of attic retraction pocket.

Results. Average age of the children was 3yr 1 month old (36.7 +- 12 months). AA was not necessary in 42.5 % that were early stage CC managed with canaloplasty plus extended tympanomeatal flap elevation without atticotomy, AA was required in the other 57.5%; 17.1% of stage II CC to visualize medial side of malleus, and all cases of stage III, IV CC that involved incudostapedial ioint. Mastoid invasion over antrum that required CWD conversion was only in 4 cases. Second look operation was required in 10%. and residual cholesteatoma was found in 8.5%. Attic ventilation was maintained in 99.5%, and persistent attic retraction pocket developed only in 2 children, which could be managed with ventilation tube insertion.

Conclusion. AA in our MILC accomplished a excellent recidivism without the concern of retraction pocket or cavity problem in congenital cholesteatoma surgery.

### TEMPORARY CANAL WALL REMOVAL IN PRIMARY INNER EAR SCHWANNOMAS AND B2 GLOMUS TYMPANICUM TUMORS

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The primary inner ear schwannoma (PIES) is a group of benign tumors which are defined by their location (modified Kennedy classification): intracochlear, intravestibular, intravestibulocochlear, transmodiolar, transmacular, tympanolabyrinthine and translabyrinthine tumors which grow towards the cerebellopontine angle. Most PIES can be managed with a wait-and-scan policy, but when deafness, incapacitating vertigo or tumor growth occurs, microsurgical resection can be offered to the patient. Different approaches are possible and depend on the tumor location, ranging from the transcanal approach to the transotic approach. The glomus tympanicum is a benign middle ear tumor originating from the glomus bodies that lie along the Jacobson's and Arnold's nerve. The glomus tympanicum can be staged by using the modified Fisch and Mattox classification. By using the surgical algorithm proposed by Mario Sanna each tumor stage is associated with a different surgical approach. In B2 glomus tympanicum tumors, the default strategy is a canal-wall up mastoidectomy with extended facial recess opening combined with subfacial recess tympanotomy without embolization. However, this type of tumor is highly vascularized and can produce excessive bleeding during surgery leading to subtotal resection or potential complications due to low visibility. On the other hand, the subfacial recess tympanotomy requires extensive retrofacial drilling which can be time-consuming and does not provide excellent exposure of the hypotympanum. Our department already reported feasibility and safety of the temporary canal wall removal technique in cholesteatoma cases. The technique involves creating a wide facial recess approach and cutting the canal wall with an oscillating saw inferiorly at the level of the tympanic bone and anterosuperiorly at towards the zygomatic root. After tumor resection the canal wall can be repositioned and fixated using hydroxyapatite bone cement.

The aim of the present study is to report our experience with temporary canal wall removal in intracochlear schwannomas and B2 glomus tympanicum tumors.

Material and Methods: We performed a retrospective review on 7 consecutive cases with an intracochlear schwannoma (n=1) and B2 glomus tympanicum (n=6) who underwent canal wall up mastoidectomy with temporary canal wall removal. We reviewed complciations such as cholesteatoma, recurrence, facial nerve palsy, etc. Total resection was achieved in all cases. In the B2 glomus tympanicum cases minimal bleeding was observed during surgery, which was easily controlled by bipolar cautery. None of the patients had any temporary or permanent facial paresis or palsy. No complications were observed such as granulation formation, extrusion of the canal wall or formation of cholesteatoma. The temporary canal wall removal technique is a versatile and safe strategy to easily approach the hypotympanum and promontory. It avoids the need for the retrofacial approach when accessing the hypotympanum and avoids the need for the transotic approach (and thus the need for blind sac closure and abdominal fat harvesting) in selected primary inner schwannomas. In case of intact cochlear function (especially in B2 glomus tympanicum cases) it enables preservation of the ossicular chain.



#### VESTIBULAR NEURECTOMY: RETROSIGMOID OR RETROLABYRINTHINE APPROACH?

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**Objective:** The retrosigmoid (RS) approach and the retrolabyrinthine (RL) approach are two main classical surgical approachs for vestibular neurectomy. However, their advantages and disadvantages have not been well documented. The aim of this study is to compare in several aspects.

Methods: From 2009 to 2014, a retrospective analysis of 63 Meniere's disease patients who underwent vestibular neurectomy was presented. RS approach was performed in 40 cases, and RL approach in 23 cases. The operation time, distance between the dura and the facial-acoustic nerve bundle, operative visual field exposed, cerebellum compression, and the rate of postoperative complication were compared.

Results: The results showed that the average operation time for RS approach was similar to that for RL approach. In RL approach, In RL approac the average distance between the dura and the facial-acoustic nerve bundle was significant shorter than that of RS approach. Moreover, less cerebellum compression was needed in RL approach for vestibular neurectomy. However, RS approach provided better visualization of the cerebellopontine angle for vestibular neurectomy. There was not statistically significant difference between the two approachs in the rate of postoperative complication.

Conclusions: RL approach for vestibular neurectomy could need similar operation time, and offer shorter distance to the facialacoustic nerve bundle, sufficient operation field, less cerebellum compression and equal outcomes in the treatment of MD when compared with RS approach.

## TREATMENT

#### DIFFICULTIES OF PSYCHOLOGICAL THERAPY IN PATIENTS WITH MENIERE'S DISEASE

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Objective: The Aim of this study is to report the difficulties of psychological therapy and the effectiveness in the reduction of stress and depression among patients with Meniere's Disease.

Material and Method: Thirty-eight patients with symptoms of Meniere's Disease were followed in our clinical interview; five of these patients underwent psychological assessment with cognitive behavioural therapy (C.B.T). We have used The Questionnaire of Stressed Survival Situations prepared by Zenab Mahmoud Shugair, before and after the treatment by C.B.T.

The following activities were performed in the therapy: Behavioural Experiments, Thought Records and relaxation.

Results: There are statistically significant differences between the average level of stress before and after the treatment by C.B.T. **Difficulties are:** 

- The patients do not perceive the underlying psychology that the therapists do.
- They make defence type rationalization with hyperactivity, which can make it difficult to support therapeutic setting.
- Absence from psychotherapy sessions due to the high frequency of episodes of the illness.
- Positive transfer towards their ENT doctor rather than towards their psychologist.

**Conclusion:** The Medical treatment of Meniere's Disease is often ineffective, research presented evidence that psychological factors played a significant role in the management of this disease.

Psychological assessment, consultation, and CBT may prove beneficial to the overall well being of the patient and decrease stress, due to the negative influence of the vertigo and tinnitus on his guality of life.

Key-words: Meniere's Disease - stress - cognitive behavioural therapy - quality of life.

### INTRACOCHLEAR DRUG DELIVERY BY INJECTIONS THROUGH THE ROUND WINDOW MEMBRANE: MEASURES TO IMPROVE DRUG RETENTION

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**Objective:** To develop methodology to apply drugs quantitatively to perilymph of the ear. Intratympanic application of drugs to the inner ear often result in variable drug levels in perilymph and can only be used for molecules that readily permeate the round window (RW) membrane. Direct intracochlear and intralabyrinthine application procedures for drugs, genes or cell-based therapies by-pass the tight boundaries at the round window, oval window, otic capsule and the blood-labyrinth barrier. However, the inner ear of animals is held under a positive hydrostatic pressure maintained by communication with cerebrospinal fluid (CSF). Perforations that release inner ear pressure allow influx of CSF through the cochlear aqueduct causing volume flow towards the perforation site. The resulting flow displaces injected drug solutions, washing them out into the middle ear. Methods: Two markers, fluorescein or fluorescein isothiocyanate (FITC)-labeled dextran, were used to quantify how much of an injected substance is retained in cochlear perilymph following an intracochlear injection. We evaluated whether procedures to mitigate fluid leaks improved marker retention in perilymph.

Results: Almost all procedures to reduce volume efflux, including the use of gels for internal sealing and glues for external sealing of the injection site, resulted in improved retention of the marker in perilymph. Adhesive on the RW membrane effectively prevented leaks but also influenced fluid exchange between CSF and perilymph. **Conclusion:** Drugs can be delivered to the ear in a consistent, quantitative manner using intracochlear injections if care is taken to control the fluid leaks that result from cochlear perforation.


# **VESTIBULAR TESTING**

#### ABNORMALITY OF DOLLS' EYES RESPONSE TO HEAD TILT IN ROLL IN PATIENTS WITH MENIERE'S DISEASE

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### Introduction: The most notable histopathological feature of Meniere's Disease (MD) is, by definition as the endolymphatic hydrops (EH). Despite initially the EH involves the whole inner ear system, there are few reports of otolith dysfunction due to the EH in MD patients [1, 2].

To detect the EH in the otolith organs, we investigated the otolithic nature based on dolls' eyes response to head tilt in roll (dolls' eye) in MD patients.

Patients and Methods: Dolls' eye was investigated in 16 MD patients in age from 16 to 67 year-old, visiting our clinic.

The dolls' eyes maneuver in head tilt in roll (dM) was applied in MD patients. All patients were instructed to sit on the couch in the upright position, to fixate examiner's nose by the dominant eye, during dM. The head was smoothly tilted from the upright position to the right shoulder about 10-15 degrees firstly and after that, the head recovered to the upright, passively. To the opposite side tilt was done in the same way. All dMs were performed in the light. Patients were asked not to blink during dM as few as possible. Either right or left eye, which is not dominant eye, and its eye movements were monitored by using a modified Frenzel glasses with an infrared camera. Each side of the glasses was able to open the eye cover so that the dominant eye can fixate the examiner's nose. Recorded eye movements (6 out of 16 patients) were analyzed using custom made software running on the NIH Image Program [3] that is widely used in the world. And we asked how they feel during dM.

Results: The smooth dolls' eye, so called ocular counter-rolling response (OCR), was observed in 6 normal subjects, though, MD patients showed quite strange eye movements. There can be classified them into three main types in MD patients, as follows: 1) similar to OCR but something different 2) torsional nystagmus to the tilted side 3) almost standing still.

MD patients all declared that it was difficult to fixate examiner's nose despite the instruction, since they all felt strange eye movements and/or sick.

**Discussion and Conclusion:** We could not realise which the vestibular organs actually play a main role of these strange eye movements in MD patients. It is reported that some of MD patients showed abnormal ocular torsion (AOT) in the upright position that can be contributed otolith dysfunction because of the EH [1]. And also some report aurque nowadays ocular tilt reaction (OTR) in patients with peripheral vestibulrar disoreder, MD [4], as well. AOT and/or OTR may drive an incomplete response to dM and produce strange eye movements. According to this, in cases of MD, dM can be useful to detect strange eye movements noninvasively. Therefore, we emphasise that dM may be able to detect the EH in MD patients.

#### COMPARATIVE EVALUATION BETWEEN CALORIC TEST, VEMP AND DDPAOE IN DIAGNOSING MENIERE'S DESEASE

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Objective: To estimate the sensitivity and specificity of DDPAOE and Vestibular Evoked Myogenic Potentials in comparison with caloric test in diagnosing Meniere Disease MD.

Method: Data were retrospectively collected from 850 consecutive patients who underwent vestibular tests. Among them, 78 patients were diagnosed as having unilateral definite MD.

The sensitivity and specificity of each test were evaluated. The results of each test were compared with hearing level and staging of MD.

**Results:** The sensitivity and specificity of DDPAOE were 65%. But VEMP and caloric test are respectively 52% and 47%. **Conclusion:** The sensivity and specifity of DDPAOE in diagnosing of MD are higher than VEMP and caloric test

## FUROSEMIDE LOADING VESTIBULAR EVOKED MYOGENIC POTENTIALS CAN DETECT HAVING ENDOLYMPHATIC HYDROPOS -UP-**TO-DATE EXPERIENCE-**

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**Objective:** We previously reported that the p13-n23 peak-to-peak amplitude in vestibular evoked myogenic potential (VEMP) increased after furosemide administration in the patients with Meniere's Disease. The positive ratio is 40%, therefore, the clinical usage is difficult to detect the endolymphatic hydrops. The procedures to recording VEMP have been developed since then. The first is tone-burst stimulation were used to record VEMP instead of click sound. The second is to neglect variability of muscular tonus, amplitude were evaluated after normalization by integrated EMG or RMS value of EMG. We adjust the examination to apply up-todate clinical setting.

Methods: The subjects were 10 patients with Meniere's Disease and 2 patients with endolymphatic hydrops (the endolymphatic hydrops group). They consisted of 4 males and 8 females and their ages ranged from 24 to 59 years. For the control group, 10 ears of 6 normal healthy volunteers were used. They consisted of 3 males and 3 females and their ages ranged from 28 to 42 years. The peak-to-peak amplitudes of VEMP were recorded before (AB) and after (AA) 20mg of furosemide administration. The improved ratio is calculated by the following formula:  $IR = 100 \times (AA-AB)/AB$ . In this study, the amplitude was normalized as the raw amplitudes divided by the integral EMG value during 20 msec before sound stimuli. Tone burst sound stimuli of 105 dBSPL and 500Hz were delivered from an ipsilateral headphone.

**Results:** The mean amplitude before and after administration were  $0.091 \pm 0.032$  and  $0.070 \pm 0.021$  respectively in the control group. There was not significant difference (p>0.05: Wilcoxon sinned-ranks test). The mean improved ratio was  $-15.3 \pm 25.6$  % in the control group. In the endolymphatic hydrops group, the mean amplitude before and after administration were 0.079 + 0.047 and 0.096 + 0.052 respectively. The amplitude was significantly improved after furosemide administration (p=0.034: Wilcoxon sinned-ranks test). The mean improved ratio was  $23.2 \pm 50.6$  % in the endolymphatic hydrops group. Conclusion: When cutoff value was defined normal upper limit (35.9%), sensitivity was 41.7% and specificity was 100%. When the value was defined 22.0%, sensitivity was 63.6% and specificity was 90%, thus it was thought that the furosemide loading VEMP is useful in the clinical diagnosis of endolymphatic hydrops.





## IS THE CAUSE OF A VERTIGO ATTACK MENIERE'S DISEASE OR VESTIBULAR NEURITIS ? OBJECTIVE MEASUREMENTS GIVE THE ANSWER

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Aim and Introduction: When a patient arrives at a clinic with an acute attack of vertigo, a major question facing the clinician is; what is the cause of this attack? Is it due to Meniere's Disease (MD) or due to vestibular neuritis (VN)? Both cause severe attacks with vertigo and nystagmus. but the treatment and therapeutic progression and the outcomes for these two causes are very different. How then is it possible to distinguish between them? Caloric testing can give evidence about the level of horizontal canal function but the variability of the caloric test is high and giving a caloric test to a patient in the midst of a major attack of vertigo is difficult, unpleasant and distressing for both the patient and the clinician and many patients refuse to undergo such distressing testing.

Patients and Methods: Here we report two patients as examples of patients diagnosed with MD and two patients with VN who arrived at the MSA Clinic in Cassino with very similar vertigo attacks, in order to show how, by applying new validated clinical tests it is possible to simply and quickly distinguish between MD as opposed to VN in a way which was fast and which was not distressing for the patient or the clinician.

The first test is the video head impulse test (vHIT - MacDougall et al 2009), the second new test is the ocular vestibular-evoked myogenic potential (oVEMP) of mainly utricular. The results of these tests is different for an MD attack as opposed to a VN attack. **Results:** On the basis of physiology, pathophysiology, previous publications of patient results, we know that vestibular neuritis causes reduced or absent response of semicircular canal neurons, resulting in reduced VOR gain. In contrast in MD at attack, horizontal canal dynamic function is normal or even enhanced (Manzari et al. 2011). So if in a patient at attack vHIT indicates reduced VOR gain for head rotations towards the affected ear, then it is likely that it is VN not MD.

It is established that in vestibular neuritis the oVEMP n10 response is reduced or absent beneath the eye opposite the affected ear (Iwasaki et al. 2009., Manzari et al. 2010). In MD attack the oVEMP n10 is usually enhanced (Manzari et al. 2010). So if in response to Fz BCV, the two n10 potentials are asymmetric with the contralateral n10 smaller or absent, then it is likely that to be VN.

Could it be that the probable MD patient had a stroke? since the new HINTs protocol describes the presence of normal head impulse test, together with nystagmus (and skew deviation), is a sensitive and specific indicator of central stroke (Newman Toker et al 2008; Kattahet al 2009) and the probable MD patients here has two of those indicators. It is unlikely because the other usual otological tests - suppression of nystagmus by visual fixation, absence of gaze evoked or direction changing nystagmus, only moderate postural instability –all point to a peripheral cause rather than a central one.

**Conclusion:** The results from these new two tests are complementary since one is investigating semicircular canal function in the superior vestibular nerve and the other is investigating otolith function in superior vestibular nerve. They answer the question as to the cause of the attack.

## ISOLATED AND COMBINED SEMICIRCULAR CANAL DYSFUNCTION IN PATIENTS WITH UNILATERAL VESTIBULAR SCHWANNOMA

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Introduction and Aim: To examine the impact of vestibular schwannoma (VS) on the vestibular system, its function is normally assessed using electronystagmography (ENG) that includes oculomotor, rotary chair and caloric testing. Recently, supplementary vestibulo-ocular reflexes (VOR) of all 3 individual semicircular canals (SCC) can be assessed by acquiring fast eye movements responses during a head impulse. By video recording of eye fixation/saccades with 100 images per second (video Head Impulse Testing, vHIT), it is possible to obtain not just overt, but also covert correction saccades to assess an absence of the VOR.

Since standard caloric and rotary chair tests are specifically focused on the horizontal SCC, the aim of the present study was to investigate the clinical impact of vestibular schwannomas on the vertical, i.e. posterior and anterior, SCCs functionality, in particular. Results will elucidate its' surplus value, and reveal possible clinical diagnostic implications and might improve patient counseling. Patients and Methods: Patients (n=86) with a unilateral vestibular schwannoma were included in a retrospective study. Multi-channel ENG recordings were performed to assess the horizontal canals using conventional bithermal caloric water irrigation testing. Additionally, VORs were obtained by video Head Impulse Testing (vHIT) to individually assess isolated horizontal, but also both vertical (superior and anterior) SCCs.

unilateral vestibular loss. With vHIT, it was possible to evoke responses in all 6 semicircular canals in 78% of the patients. In 61% of the patients, only one SCC was affected: lateral canal only: 25%; posterior canal only: 36%. None of the patients with VS reveal a single anterior SCC lesion, nor in combination with the posterior canal. In all other patients, two or more canals were affected, in which the lateral canal was always involved (lateral + anterior: 7%, lateral + posterior: 11%, lateral + anterior + posterior: 21%). The present results show that only caloric assessment, did not provide sufficient information about the vestibular function. Only in 64%, the lateral canal is part of a complete vestibular loss. Data analysis also showed that normal or asymmetrical caloric test outcomes show false negative results in about 11% of all patients, who have a posterior canal lesion. In conclusion, vHIT has a surplus value in the assessment of patients with vestibular schwannoma and is complementary to caloric testing, since it provides additive and useful information about the functionality of all three SCCs, especially regarding the posterior SCC. Following from this, its implications are obvious and will be further addressed regarding to practical counseling and clinical management.

#### MATURATION OF SUBJECTIVE VISUAL VERTICAL IN CHILDREN

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Introduction: The attraction of the Subjective Visual Vertical (SVV) to the side of rod presentation has already been described in adults and is potentially related to visual dependency. The aim of this study to evaluate this phenomenon in children and to analyze the effect of sex and age. Materials and Methods: This retrospective study included 601 children and teenagers aged between 4 and 19 years. All subjects underwent a SW evaluation included in a complete balance workup. SW was measured by presenting a phosphorescent rod 12 times in total darkness with a 45° deviation from the vertical alternatively on the left and the right. The patient was asked to replace the bar vertically with a remote control. **Results:** On average, SW at each iteration was tilted to the side of the rod presentation. The cumulative tilt to the side of presentation after 12 measures was higher in the 4-7 years age group and decreased progressively with age  $(25 \pm 2.2^{\circ} \text{ in 4-7 years group, mean} \pm \text{SEM}, n=109 \text{ versus})$  $5 \pm 1.4$  in 15-19 years, n=204, p<0.001, ANOVA). The cumulative tilt was higher in girls than in boys in the 15-19 years group (8 ± 2.5, n=104) in girls versus  $2 \pm 1.2^{\circ}$  n=100 in boys, p<0.001, ANOVA). This phenomenon appeared to be independent from the type of vestibular disorder. **Conclusion:** Young children are highly attracted to the side of rod presentation during SW measurements. This phenomenon gradually disappears with age but a significant difference appears between genders suggesting a hormonal role.

- **Results and Conclusions:** Standard ENG revealed a significant asymmetry in 68% of the patients, i.e. severe hyporeflexia or a complete



### THE PATIENTS WITH MENIERE'S DISEASE RESULTS IN THE DISCREPANCY BETWEEN VIDEO HEAD IMPULSE TEST AND CALORIC TESTING

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Introduction: Video head impulse test (vHIT) was established in 2009 and has been widely performed for clinical examination. It was reported that the results of vHIT were different from those of the caloric testing in some cases with Meniere's Disease. The aim of this study was to clarify whether the discrepancy exists.

Subjects and Method: The subjects consisted of 6 cases of unilateral Meniere's Disease, 5 cases of vestibular neuritis and a case of Ramsay Hunt syndrome. The vHIT were examined using ICS Impulse. When VOR gain was lower than 0.8, we defined the result as abnormal. CP% was calculated from monothermal caloric testing. When CP% exceeded 25%, we defined a result to be abnormal. Result: While abnormal results in caloric testing were shown in 5 cases of vestibular neuritis, vHIT showed abnormality except one case of them. One case of Ramsay Hunt syndrome showed an abnormality on both caloric testing and vHIT. On the other hand, abnormal results on caloric testing were shown in 4 cases of Meniere's Disease and vHIT showed the abnormal result on 1 case among them.

**Conclusion:** The discrepancy between the results on vHIT and those on caloric testing was confirmed. We suggested the following mechanism: endolymphatic hydrops causes the enlarged ampulla portion, and then convection flow during caloric stimulation decrease. When sensory cell or cupula are not damaged, vHIT shows normal even in enlarged ampullar portion.

#### VESTIBULAR FUNCTION IN PARTIAL AND TOTAL DEAFNESS

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Aim: The study aims at assessing and comparing the vestibular function in patients with low frequency residual hearing versus patients with total deafness. The question that is raised is if and to what extent hearing preservation at low frequency coexists with better vestibular status and better responses in vestibular tests.

Materials: All the patients with bilateral profound deafness, between 20-50 years old, before being implanted with cochlear implant, were divided into four groups according to the preservation of residual hearing: Group 1 – patients with partial deafness dedicated to PDT-EC (partial deafness treatment - electrical complement), Group 2 - patients with partial deafness for PDT-EAS (partial deafness treatment - electro-acoustic stimulation), Group 3 - patient with partial deafness for PDT-ES (partial deafness treatment - electric stimulation), Group 4 - patients with total deafness.

Methodology: The patients underwent cVEMP, oVEMP, vHIT examination and fulfilled the questionnaire to assess the vestibular symptoms.

Results and Conclusions: Patients with partial deafness achieved better responses in VEMP tests. However, the preliminary study and results showed no significant difference between PDT-EAS and PDT-EC group and that the intensity of vestibular symptoms was independent on the type of hearing loss.

## VESTIBULAR NEURITIS ACCORDING TO VHIT TESTINGS. CLINICAL ENTITIES AND PROGNOSTIC FACTORS

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Introduction: Vestibular neuritis (VN) usually involves the superior vestibular nerve thus defining superior vestibular neuritis (SVN). Conversely, inferior vestibular neuritis (IVN) has also been reported. Because the video head impulse test (VHIT) is able to test vestibulo-ocular reflex (VOR) from each semi-circular canal, VHIT can be an interesting tool in differentiating IVN showing a deficit of the posterior semi-circular canal (SCC) from SVN showing a deficit on both the superior and lateral SCC. The aim of this study was to evaluate the use of VHIT in differentiating IVN from SVN in their initial clinical presentation and to identify clinical entities according to outcomes.

Patients: From 2010 to 2013, a prospective study was conducted in a tertiary referral center including all consecutive adult patients admitted with a first vestibular or cochleovestibular syndrome mimicking VN, associated with SCC deficit(s) on VHIT. Cardiovascular risk factors (CVRF) were recorded. Initial clinical presentation was compared with recovery on VHIT between groups. **Results:** Sixty-two patients were included in this study and were split in three groups. Patients in group I (n=28) had a VHIT deficit on the posterior SCC (IVN) whereas patients in group II (n=24) and III (n=10) had a VHIT deficit on both superior and lateral SCC, SVN (group II) and on the 3 SCCs (group III) respectively.

Initial clinical presentation was different among the three groups. In Group I (IVN) patients had postural imbalance, nausea/vomiting and a torsional and down-beating nystagmus. Half of patients in group I had deafness and the other half had no cochlear symptoms. In group II (SVN), all patients had a controversive torsional nystagmus associated with segmentary deviation on the side of the pathologic vestibule and without auditory symptoms. Group III patients had a clinical presentation similar to that of group II except that twenty percent (2/10) of patients experienced hearing loss. 39% of patients without cochlear symptoms had none CVRF whereas all patients with auditory symptoms had at least one CVRF (p<0.05). Outcomes at 3 months showed different types of recovery according to the three groups. In group I (IVN), patients without cochlear symptoms experienced 100% recovery on VHIT whereas deaf patients had a 46% recovery on VHIT (p<0,05). In Group II and III, patients never experienced a total recovery on VHIT (74% and 44% respectively). Recovery rates on VHIT were significantly inferior for patients with cochlear associated symptoms (p < 0.05).

Conclusion: Among patients with IVN, two different clinical presentations with or without auditory symptoms were observed and exhibited two different pattern of recovery. Patients without auditory symptoms had all good outcomes with complete recovery of VHIT whereas, patients with auditory symptoms had worst outcomes on VHIT and deafness. Concerning SVN, the outcome on VHIT is significantly worst that that of isolated IVN without cochlear symptoms. As for SVN which involves superior and lateral SCC deficits, a microvascular etiology may be suggested.



#### WHITE & GRAY MATTER DIFFERENCES BETWEEN VISUAL VERTIGO PATIENTS AND HEALTHY CONTROLS: PRELIMINARY RESULTS.

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Introduction and Aim: Visual vertigo (VV) is a complex syndrome where patients experience severe dizziness due to disorienting visual environments (e.g. supermarket aisles, crossroads). This could be due to a mismatch at specific brain regions where the integration of visual, vestibular and proprioceptive signals takes place. The aim of this pilot study was to gain insight in the process of mismatch or hampered neuroplasticity in W patients. We compared patients with a healthy group and investigated differences in the cerebellar and visual pathways in the brain.

Materials and Methods: For this pilot study, five W patients (1 male, mean age: 48.4years) and five healthy control subject (1 male, mean age: 51.1 years) were included. Multi-shell high angular resolution diffusion weighted (DW) data were acquired on a 3T MRI scanner using a 32-channel head coil for all participants. Diffusion tensor imaging (DTI) data were analyzed by means of tractography. In this pilot study, we focused on cerebellar and visuospatial pathways such as cerebellar peduncles, inferior frontoorbital fasciculus (IFOF) and inferior longitudinal fasciculus (ILF). Voxel-based morphometry (VBM) was also performed to analyze whole-brain gray matter.

Results: We found statistically significant lower values in diffusion measures for the W patients in the visuospatial network, but statistically significant higher values for the cerebellar network. Furthermore, VBM analysis showed a significant gray matter decrease in the left inferior occipital lobe (p<0.001, uncorrected) and the right angular gyrus (p<0.001, uncorrected).

Conclusions: To our knowledge, this is the first study to use diffusion imaging methods in this specific subgroup of vestibular patients. Furthermore, we show a relation between parameters representing brain connectivity and clinical symptoms of vertigo, defining consequently biomarkers in the brain for visual vertigo, a disease that is hard to objectify

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