



The Neuro-Otology Society of Australia

***Abstracts of the 27th Annual Clinical and
Scientific Meeting***

Friday 3rd, Saturday 4th, Sunday 5th November 2017

Royal Prince Alfred Hospital, Sydney

Contents

Author	Title	Page
Bradley	Comparison of static and dynamic tests of otolith function	3
Brown	The Guinea Pig Endolymphatic Duct with Labyrinthitis	4
Chen	Spontaneous nystagmus characteristics in acute vestibular syndrome: vestibular neuritis and pontine-cerebellar stroke	5
Chiarovano	An embedded researcher : one year after	5
Choi	Acute Transient Vestibular Syndrome Prevalence of Stroke and Efficacy of Bedside Evaluation	6
Colebatch	Location and phase effects on ocular and cervical vestibular-evoked myogenic potentials (VEMPs) evoked by bone-conducted stimuli at midline skull sites.	7
Curthoys	Utricular responses to bone conducted vibration	8
Fujimoto	Noisy galvanic vestibular stimulation induces a sustained improvement in body balance in patients with bilateral vestibulopathy	9
Gerraty	Transient vertigo preceding vestibular neuritis	10
Hannigan	The dissociation of vHIT and Calorics, how it works in the clinic	11
Hornibrook	Scary and Difficult Cases: A Time for Reflection	12
Hoskison	Canal and Otolith Function Tests Before and After Cochlear Implantation	12
Iwasaki	Frequency characteristics of postural sway in bilateral vestibulopathy and persistent postural and perceptual dizziness	13
Katz	The diagnostic accuracy of dizziness presentations to a specialised eye and ear Emergency Department	14
Khan	The Role of the Otoliths in Vestibulo-ocular Reflex Adaptation	14
Lim	Mini ear organoids – how do they compare with human vestibular hair cells?	15
McNeill	A case of Many Ears disease	16
Mossman	Personality characteristics of patients with persistent perceptual postural dizziness; a comparison with BPPV	16
Pastras	Suppression of the Vestibular Short Latency Evoked Potential with Electrical Stimulation of the Central Vestibular System	17
Poppi	Calcium in balance: GCaMP imaging in the crista ampullaris	18
Power	Toward objective clinical diagnosis of cerebellar ataxia	19

Rahmann	Vestibular dysfunction is poorly identified in people admitted to sub-acute rehabilitation following an injurious fall	20
Reid	Vertigo in the Emergency Department: new bedside tests	21
Reynolds	Patient Presentation....'a puff of hot air'	21
Rinuado	VOR rehabilitation RCT using StableEyes: Preliminary data	22
Rosengren	Vestibular projections to the splenius capitis neck muscles in humans	24
Strupp	Cerebellar dizziness and cerebellar ocular motor disorders: diagnosis and current pharmacotherapy	25
Strupp	Peripheral vestibular disorders: a quick update	34
Taylor	Improving the Specificity of VEMP testing in SSCD: Trial by oVEMP	39
Todd	A new measure of vestibulo-cerebellar function?: the vestibulo-cerebellar evoked potential (VCEP)	40
Vartanyan	Garden Terror – Case Series Of Twenty Eight Serious Ear Injuries Caused By Yucca Plants	41
Watson	The Vestibular System and Sleep	42
Wellings	Reduced neurofilament protein expression and accumulation of lipofuscin in the lateral vestibular nucleus in Parkinson's disease; a new insight into postural instability?	42
Williams	Who said there is no treatment for Tinnitus?	43
Yamsuan	The Effects of Habitual Spectacle Use and Visual Acuity on the Video Head Impulse Test	44

Comparison of static and dynamic tests of otolith function

Bradley J, Young AS, Pogson J, Taylor RL, Reid N, Nguyen V, Halmagyi GM, Welgampola MS
Institute of Clinical Neurosciences, RPA Hospital Camperdown NSW

Introduction

The Ocular Vestibular Evoked Myogenic Potentials (oVEMP) and Subjective Visual Horizontal (SVH) testing represent two non-invasive techniques of assessing human otolith function. We sought to compare the results of these two tests of predominantly utricular function, when performed on the same day for a group of patients who presented to a neuro-otology outpatient facility.

Methods

A retrospective analysis was performed on 900 patients on whom both SVH, Cervical VEMP (CVEMP) and OVEMPs had been performed. SVH was tested with both eyes viewing an illuminated bar in a dark room; an average of 10 trials was used. Ocular VEMPs were recorded in response to 105 dB nHL (140 dB peak SPL) 0.1ms air-conducted clicks and 20V p-p (146 dB Force Level) 1ms bone conducted taps delivered via a minishaker. Mean SVH was correlated with the asymmetry ratios for AC and BC OVEMP and CVEMP peak to peak amplitudes.

Results

A total of 219 patients had measurement of SVH and OVEMPs on the same day; 39 patients had a diagnosis of acute vestibular neuritis (VN). The Pearson's correlation coefficient between the SVH and the BC OVEMP across all 219 patients was 0.46 ($p < 0.001$). When subjects with acute vestibular neuritis ($n = 39$) were separately correlated the coefficient rose to 0.55 ($p < 0.001$). The correlation coefficient between the SVH and the AC OVEMP across all patients ($n = 135$) was 0.38 ($p < 0.0001$). The coefficient increased to 0.5 when subjects with acute VN ($n = 23$) were correlated. In a smaller group of subjects ($n = 60$) who underwent cVEMP testing and SVH on the same day, the correlation coefficient between AC CVEMP asymmetry and SVH was 0.27 ($p = 0.036$) while for BC CVEMPs, the coefficient was 0.29 ($p = 0.025$).

Conclusion

There are moderate, highly significant correlations between SVH and OVEMP asymmetry when tested on the same day, greater for bone conducted OVEMP than air conducted OVEMP. As expected, subjects with acute vestibular neuritis, which predominantly affects the superior vestibular nerve demonstrate more powerful correlations. Weaker correlations exist between SVH and the CVEMPs which assess saccular function.

The Guinea Pig Endolymphatic Duct with Labyrinthitis

Daniel Brown, Ljiliana Sokolic

The University of Sydney, Sydney Medical School

Background: Most theories of Meniere's disease involve immune mediated damage of the endolymphatic sac resulting in chronically poor absorption of endolymph, and endolymphatic hydrops. There are several potential, yet flawed, animal models of Meniere's disease, one being antigen presentation to the inner ear perilymph, where endolymph volume increases over 2 weeks, recovering thereafter. Whilst the immunological activity of the sac temporarily increases following antigen presentation, things appear to recover, which is arguably why this is not a feasible model of Meniere's. **Methods:** To re-vamp this model, we have here injected various levels of lipopolysaccharide (LPS) into scala media of guinea pigs, and examined function and morphology up to 6 weeks later. Functional measurements included recording the compound action potential thresholds, cochlear microphonic, endolymphatic potential, and vestibular evoked potential. Morphological changes were assessed using light-sheet microscopy for assessment of the intact temporal bone. **Results:** Cochlea morphology varied with the concentration of LPS used, ranging from complete ossification, to moderate to severe hydrops with minimal cellular infiltration. In the week following LPS injection, the endolymphatic duct and sac were typically filled with homogenous substance, and several weeks after LPS the duct and sac were swollen and empty. **Conclusion:** Of primary importance was the ability to induce hydrops lasting longer than at least 5 weeks, with minimal fibrosis or cellular infiltration. However, there was a severe hearing loss (>50dB) in all animals following LPS, and minimal changes in vestibular function, and therefore this still does not represent a reasonable animal model of Meniere's.

This study is supported by Garnett Pass & Rodney Williams Memorial Foundation Fellowship Grant.

Spontaneous nystagmus characteristics in acute vestibular syndrome: vestibular neuritis and pontine-cerebellar stroke

L Chen, M J Todd, G M Halmagyi and S T Aw

Objective: To compare spontaneous nystagmus characteristic in vestibular neuritis (VN) with pontine-cerebellar stroke (PCS)

Method: Eye movement was recorded with search coils in 20 VN and 33 PCS. We determined spontaneous nystagmus horizontal slow phase velocity (SPV) in neutral and eccentric (horizontal 20°) gaze, as well as visual suppression.

Results: In all VN spontaneous nystagmus was unidirectional, maximal on contralesional gaze and well suppressed visually i.e. became more intense without visual fixation. In PCS spontaneous nystagmus presence and intensity were variable, present in 8/13 anterior inferior cerebellar artery (AICA) stroke, 5/17 posterior inferior cerebellar artery (PICA) stroke and 2/3 superior cerebellar artery (SCA) stroke. Gaze-evoked, direction-changing nystagmus (DCN) was uncommon. Visual suppression was not universally absent or poor, contrary to conventional wisdom.

Conclusion: Quantitative spontaneous nystagmus analysis can differentiate VN from PCS subgroups, and should be further investigated in future video-oculography study.

An embedded researcher : one year after

Elodie Chiarovano and Hamish MacDougall
Department of Psychology, University of Sydney

One year ago, we started a collaborative network between clinicians (neurologist, ENT, physiotherapist) and researchers. What is the state of this collaborative network? What do we learn from it? Do we help patients and clinicians? Moreover, Dr Chiarovano spend one year working one/two day(s) a week with one physiotherapist and one ENT surgeon. What did she do? What are the impacts on clinical practice of having an embedded researcher?

Acute Transient Vestibular Syndrome Prevalence of Stroke and Efficacy of Bedside Evaluation

Kwang-Dong Choi, Jae-Hwan Choi, Min-Gyu Park, Seo Young Choi, Kyung-Pil Park, Seung Kug Baik, Ji-Soo Kim.

Department of Neurology (J.-H.C., M.-G.P., K.-P.P.) and Radiology (S.K.B.), Pusan National University School of Medicine, Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, South Korea; Department of Neurology, Seoul National University Bundang Hospital, South Korea (S.Y.C., J.-S.K.); and Department of Neurology, Pusan National University Hospital, Pusan National University School of Medicine and Biomedical Research Institute, South Korea (K.-D.C.).

Background and Purpose—The aim of this study was to determine the prevalence of stroke and efficacy of bedside evaluation in diagnosing stroke in acute transient vestibular syndrome (ATVS). **Methods**—We performed a prospective, single-center, observational study that had consecutively recruited 86 patients presenting with ATVS to the emergency department of Pusan National University Yangsan Hospital from January to December 2014. All patients received a constructed evaluation, including HINTS plus (head impulse, nystagmus patterns, test of skew, and finger rubbing) and brain magnetic resonance imagings. Patients without an obvious cause further received perfusion-weighted imaging. Multivariable logistic regression was used to determine clinical parameters to identify stroke in ATVS. **Results**—The prevalence of stroke was 27% in ATVS. HINTS plus could not be applied to the majority of patients because of the resolution of the vestibular symptoms, and magnetic resonance imagings were falsely negative in 43% of confirmed strokes. Ten patients (12%) showed unilateral cerebellar hypoperfusion on perfusion-weighted imaging without an infarction on diffusion-weighted imaging, and 8 of them had a focal stenosis or hypoplasia of the corresponding vertebral artery. The higher risk of stroke in ATVS was found in association with craniocervical pain (odds ratio, 9.6; 95% confidence interval, 2.0–45.2) and focal neurological symptoms/signs (odds ratio, 15.2; 95% confidence interval, 2.5–93.8). **Conclusions**—Bedside examination and routine magnetic resonance imagings have a limitation in diagnosing strokes presenting with ATVS, and perfusion imaging may help to identify strokes in ATVS of unknown cause. Associated craniocervical pain and focal neurological symptoms/signs are the useful clues for strokes in ATVS.

Location and phase effects on ocular and cervical vestibular-evoked myogenic potentials (VEMPs) evoked by bone-conducted stimuli at midline skull sites.

Govender S¹, Colebatch JG^{1,2}

¹Neuroscience Research Australia, Randwick NSW 2031 and ²POW Clinical School, University of New South Wales

Govender and Colebatch (2017) showed that there were systematic changes for compressive vs rarefactive onset phase on oVEMPs evoked by midline, bone-conducted (BC) 500 Hz and impulsive stimuli applied to sites between Nz and Cz. There was much less effect on cVEMPs although these did occur for impulsive stimuli. The basis of these changes was unclear and not explained by changes in the linear acceleration of the skull. We have explored this further using skull sites from Nz to Iz and also measuring pitch, roll and yaw rotational acceleration. We confirmed the phase inversion for compressive onset stimuli occurring at AFz and Fz for oVEMPs, associated with shortening of latency. Roll and yaw were small for all sites. Pitch was largest for Nz and Iz or Pz but did not predict the polarity of oVEMPs. The cVEMP findings were consistent with a role in maintaining the head upright. While oVEMP polarities for Iz and Nz are those expected for the linear VOR, the findings at AFz and Fz are not. A direct action of both types of BC stimuli on utricular hair cells, specifically when applied at AFz and Fz, could explain our findings (Curthoys & Grant, 2015).

References

- Curthoys IS, Grant JW (2015). How does high-frequency sound or vibration activate vestibular receptors? *Exp Brain Res* 233:691-688.
- Govender S, Colebatch JG (2017). Midline sagittal effects on bone-conducted cervical and ocular vestibular evoked myogenic potentials. *J Appl Physiol* 122:1470-1484.

Utricular responses to bone conducted vibration

Ian S. Curthoys¹ , JW “Wally” Grant² , Chris J. Pastras³ , Daniel J. Brown³

1 Vestibular Research Laboratory, School of Psychology, the University of Sydney, NSW, Australia.

2 Department of Biomedical Engineering and Mechanics, Virginia Tech, Blacksburg Virginia 24061 USA

3 The Menière's Laboratory, Sydney Medical School, The University of Sydney, Sydney, NSW, 2050, Australia

Question. How can the utricular macula respond to such high frequencies used to elicit vestibular evoked myogenic potentials in human patients, given that the utricular system has such a high mass of otoconia and high viscosity gel layer utricular membrane? Physiology shows utricular afferent neurons with irregular resting discharge are activated by high frequencies of bone conducted vibration (2000Hz). Translating the basic physiology to the clinic:

1. A special band of receptors on the utricular macula, called the striola, has increased concentration of type I receptors with short stiff cilia. Type I receptors have been demonstrated to respond up to high frequencies of displacement of their cilia (Songer and Eatock 2013)
2. Utricular afferents with irregular resting discharge are activated by sound and vibration and form calyx synapses on these type I receptors
3. The action potentials in the irregular afferents activated by sound and vibration are locked to a particular phase of the stimulus waveform, up to frequencies of 2000Hz.
4. So each cycle of the waveform is the effective stimulus – it must be deflecting the hair bundles of the receptors once per cycle in order to elicit this tight phase locking.
5. That is confirmed by recording of a vestibular (utricular) microphonic to the BCV (or sound) stimulus up to high frequencies, showing that the utricular receptors are getting deflected once per cycle. It is stressed that this without any input from cochlear receptors. (*Pastras et al. Hearing Research 2017,354:38-47*)
6. Direct measures of utricular macula movements show that the macula moves up and down during BCV stimulation (and air conducted sound) up to frequencies of thousands of Hz.
7. The movements are very small but *in vitro* studies (Geleoc et al 1997) have shown that individual vestibular receptors have thresholds of nanometers of displacement, similar to the thresholds of cochlear receptors
8. Grant and Curthoys (*Hearing Research 2017,353:26-35*) have suggested that the utricular macula operates as an accelerometer and a seismometer - at low frequencies the otoconia move relative to the receptor cell body (accelerometer mode), but at high frequencies the otoconia are stationary and the receptors move relative to the otoconia (seismometer mode).
9. In both cases the hair bundles are deflected relative to the cell body so the receptors are activated at low (accelerometer) and at high (seismometer) frequencies.

10. Modelling shows that such a “dual mode” of operation is consistent with the thresholds of neurons as BCV frequency is increased.
11. To bring this physiology back to human VEMPs: 500Hz mastoid vibration of healthy human subjects causes small eye movements with horizontal vertical and torsional components, consistent with utricular nerve activation and VEMPs are the EMG precursors of those eye movements.

Research supported by Garnett Passe and Rodney Williams Memorial Foundation Project grants. Thanks to Ann Burgess for her continued excellent help.

Noisy galvanic vestibular stimulation induces a sustained improvement in body balance in patients with bilateral vestibulopathy

Chisato Fujimoto MD PhD¹, Naoya Egami MD PhD¹, Takuya Kawahara PhD², Yukari Uemura PhD², Yoshiharu Yamamoto PhD³, Tatsuya Yamasoba MD PhD¹ and Shinichi Iwasaki MD PhD¹

¹ Department of Otolaryngology and Head and Neck Surgery, Graduate School of Medicine, The University of Tokyo

² Biostatistics Division, Clinical Research Support Center, The University of Tokyo Hospital

³ Educational Physiology Laboratory, Graduate School of Education, The University of Tokyo

Abstract

Objective: To determine whether noisy galvanic vestibular stimulation (nGVS) has a post-stimulation effect on the improvement in body balance in patients with bilateral vestibulopathy (BV).

Methods: Thirteen BV patients underwent two nGVS sessions. In each session, the BV patients received nGVS for 30 min and were monitored without stimuli for 6 h. Two-legged stance tasks were performed with eyes closed with and without nGVS, and parameters related to postural stability were measured using posturography. Subjective improvement of body balance was also scored.

Results: In each session, the mean velocity of the movement of the center of pressure was significantly improved for 6 h after the cessation of the stimulus. The subjective symptom of body balance was also improved during the post-stimulation effect of nGVS.

Conclusions: nGVS could lead to the improvement in postural stability that lasted for several hours after the cessation of the stimulus in BV patients, especially in the parameter of velocity.

Transient vertigo preceding vestibular neuritis

Richard Gerraty; richard.gerraty@monash.edu

Gerraty RP^{1,2}, Roberts HN^{1,2}, Luthra K^{1,2}, Infeld B^{1,2}, Bruce R²

¹Central Clinical School, Department of Medicine, Monash University,

²Neurosciences Clinical Institute, Epworth HealthCare

Background: Transient vertigo preceding vestibular neuritis (VN) has been reported from Korea, exclusively as a single episode in the previous week. Such attacks have parallels with TIA, raising the possibility of a vascular mechanism for VN. We aimed to compare VN patients with and without transient premonitory vertigo to determine whether there was an age difference or VOR gain reduction difference between the two groups.

Methods: Consecutive patients with acute vestibular syndrome with onset in the previous 48 hours were enrolled. Following a detailed history and examination ICS Impulse video oculography (GN Otometrics) was performed daily during the admission.

Results: Amongst 32 patients with acute vestibular syndrome there were only four who had transient vertigo preceding the main attack. One man had two episodes lasting a few minutes in the preceding 30 days, and two more brief attacks on the day of presentation. Another man had a single episode lasting 30 minutes four days prior to presentation. One had two attacks up to 10 seconds duration, one of them while riding a bicycle 4 days before the onset of VN. One woman with Type 2 diabetes had three brief attacks in the week prior to VN presentation. Their mean age was 49 (range 33-68), v mean age 63 (NS) for the remainder (range 33-88). None of the men had vascular risk factors. The mean VOR gain on the affected side was 0.52 v 0.65 (NS) in those without transient premonitory symptoms.

Conclusion: Transient premonitory vertigo may precede an attack of presumed vestibular neuritis by several days or more. More than one attack can occur. Our numbers are small and the differences are not statistically significant, but these patients are younger and have significant VOR gain reductions unlike some much older patients with subtle acute vestibulopathy and small VOR gain reductions. Transient premonitory vertigo may have the opposite significance to TIA, and may support a viral rather than a vascular mechanism for the acute vestibular syndrome. Greater numbers of patients will need to be recruited to explore this possibility further.

The dissociation of vHIT and Calorics, how it works in the clinic.

Hannigan IP, Watson SRD, Welgampola MS

Blacktown Neurology Clinic, Blacktown NSW.

Institute of Clinical Neurosciences RPA Hospital and Central Clinical School, University of Sydney.

Background: A retrospective analysis was undertaken on 576 patients who attended a neuro otology clinic for routine vestibular function testing.

Methods: A focussed history, video head impulse testing and monothermal or bithermal caloric testing was undertaken in all subjects, unless there was a contra indication to testing.

Results: Presenting symptoms included spontaneous vertigo, positional vertigo, Imbalance or chronic subjective dizziness. For 540 patients, the results of vHIT and caloric testing were concordant. Both tests were normal in 474 subjects whose diagnoses included vestibular migraine, menieres disease, Benign Positional Vertigo and Mal de debarquement (average vHIT gain= 0.91 ± 0.02 (L); 0.99 ± 0.05 (R), canal paresis= 7.39 ± 9.19 ; range 0-28%). Fifty subjects had concordant asymmetries (average ipsilateral vHIT gain= 0.56 ± 0.16 , average contralateral vHIT gain= 0.87 ± 0.12 . canal paresis= 69.9 ± 24.47 , range-31-100%). Their diagnoses included vestibular neuritis, Menieres Disease, Vestibular Migraine, Vestibular Schwannoma. Sixteen subjects had bilateral vestibular loss with average vHIT gains of $=0.42\pm0.20$ (L); 0.41 ± 0.19 (R), peak SPV on warm caloric testing = 2.68 ± 2.08 , range 0-6 degrees (L) and 3.8 ± 3.54 range 0-10 degrees (R).

Only 36 patients showed a dissociation of results between the 2 HSCC tests. In these subjects, the vHIT gain was normal, (0.93 ± 0.06 for the left and 0.98 ± 0.07 for the Right) and the caloric test showed a canal paresis $>30\%$ ($48\pm13.8\%$). Their diagnoses included Meniere's Disease (n=27), Vestibular Schwannoma (n=2) Vestibular Migraine (n=1) and Vestibular Neuritis tested 5wks to 2 years since symptom onset (n=5). No patient had abnormal HSCC gain on vHIT with normal caloric result.

Conclusion: asymmetric caloric function in the presence of normal horizontal head impulse tests is most commonly associated with Meniere's Disease and may function as a diagnostic marker. The caloric test complements the vHIT in the assessment of vestibular disorders and is most useful in suspected endolymphatic hydrops.



Scary and Difficult Cases: A Time for Reflection

Jeremy Hornibrook, Department of Otolaryngology-Head and Neck Surgery, Christchurch Hospital, Christchurch, New Zealand (15 minutes)

Psychologists have studied the cognitive processes and biases that lead to heuristics and biases resulting in poor diagnostic decisions. Three personal cases of central pathology with delayed or potentially delayed diagnoses illustrate this. In some patients with recurrent vertigo attacks the true diagnosis can remain elusive. Three such patients are presented in whom the diagnosis remains uncertain, even with contemporary diagnostic tests.

Canal and Otolith Function Tests Before and After Cochlear Implantation

Hoskison E, Fratturo L, Pogson J, Young AS, Arguet A, Rivas C, Kong J, Birman C, Greenberg S, Welgampola MS.
Institute of Clinical Neurosciences Royal Prince Alfred Hospital Camperdown NSW2050

Background

Vertigo and imbalance are frequently described post cochlear implantation with prevalence rates from 25 to 62%. We sought to define the effect of cochlear implantation on human otolith and semi-circular canal function using a simple 5-item vestibular test battery that examines all 5 vestibular end organs in each ear.

Method

Forty (n=40) patients with a range of hearing loss aetiologies including LVAS, Menière's disease, NIHL, presbycusis, and ototoxicity were assessed before and at a mean of 213 days after surgery (range 15-1095 days). Three dimensional (3D) video head impulses (vHIT) in all semi-circular canal planes were recorded, as well as ocular and cervical vestibular myogenic evoked potentials (VEMP) to air conducted (AC) clicks and bone conduction (BC) vibration.

Results

In the operated ear, mean vHIT gains were 0.89 (HC), 0.85(AC), 0.71 (PC) before surgery and 0.79 (HC), 0.77 (AC), 0.64 (PC) after ipsilateral surgery. For the un-operated ear they were 0.87 (HC), 0.83 (AC), 0.72 (PC) before surgery and 0.86 (HC), 0.84 (AC), 0.73(PC) after contralateral surgery. A paired t-test comparing the change of mean vHIT gain, following surgery in the implanted ear and un-operated ear, yielded p values of HC = 0.020, AC=0.074 and PC=0.005.

The change in mean cVEMP asymmetry ratios (ARs) after implantation was AC=23% and BC=10%. The change in mean oVEMP ARs after implantation was AC=2% and BC=5%. A paired t-test showed no pre-operative to post-operative change in mean BC cVEMP (0.196), BC oVEMP (0.447), and oVEMP AC. A highly significant change in mean AC cVEMP was seen (0.001).

Summary

There is a significant increase in AC cVEMP asymmetry following cochlear implantation. This difference is less pronounced when using a BC stimulus. We discuss the possibilities of saccular dysfunction and spurious reflex asymmetry due to conductive hearing loss.

Frequency characteristics of postural sway in bilateral vestibulopathy and persistent postural and perceptual dizziness

Shinichi Iwasaki, Makoto Kinoshita, Chisato Fujimoto, Naoya Egami, Keiko Sugawara, Tatsuya Yamasoba

Department of Otolaryngology and Head and Neck Surgery, Faculty of Medicine, University of Tokyo

Objective: To assess the frequency characteristics of postural instability in patients with idiopathic bilateral vestibulopathy (IBV) and those in persistent postural and perceptual dizziness (PPPD) as compared to healthy subjects.

Methods; Twenty-seven patients with IBV, 66 patients with PPPD, and 194 healthy controls were included. Two-legged stance tasks were performed in 4 conditions: eyes open with and without foam rubber, and eyes closed with and without foam rubber. We normalized frequency distribution provided by maximum entropy method from 0.01 Hz to 10 Hz every 0.5 Hz about the anterior-posterior and the left-right direction. We regarded power beyond averages $\pm 2SD$ of healthy controls as abnormal.

Results: In PPPD patients, postural abnormalities were observed at lower frequencies (especially in 0.01-0.5Hz) in all four conditions, which was remarkable in the conditions without foam rubber. On the other hand, in IBV patients, postural abnormalities were seen in widespread frequencies in the conditions with eyes closed with and without foam rubber.

Conclusion: The frequency power spectrum analysis of postural stability is useful for the differentiation between PPPD and IBV.

The diagnostic accuracy of dizziness presentations to a specialised eye and ear Emergency Department

Merav Katz¹, Dr Lauren Sanders¹⁻³, Dr David Szmulewicz³, Prof Stephen O'Leary^{1,4}

1. St. Vincent's Clinical School, Fitzroy, Melbourne, The University of Melbourne, Parkville, Melbourne

2. Department of Neuroscience, St. Vincent's Hospital Melbourne, Fitzroy, Melbourne

3. Balance Disorders and Ataxia Service, The Royal Victorian Eye and Ear Hospital, Fitzroy, Melbourne

4. Department of Otolaryngology, The Royal Victorian Eye and Ear Hospital Fitzroy, Melbourne

Background: Differential diagnoses for 'dizziness' include benign peripheral and life-threatening central pathologies. Early accurate diagnosis is critical to provide treatment and mitigate missed central pathology risks. Bedside examinations are an important diagnostic evaluation component but reportedly underused. We aimed to determine the frequency of bedside examination utilisation and the diagnostic accuracy of dizziness presentations to a specialty Eye and Ear ED.

Methods: Retrospective cohort study (May 2015-Dec 2016) using ED discharge codes to capture dizziness presentations (e.g. BPPV, vestibular neuronitis). Patient demographics, bedside assessments, ED and follow-up diagnoses were recorded and compared.

Results: Record review occurred for 1274 presentations; with 'dizziness' documented in 51.2% (n=652/1274) and follow-up available in 37.9% (n=247/652). ED diagnosis confirmed at follow-up in 64.4% (n=159/247) and revised in 35.6% (n=88/247). Undifferentiated dizziness was the most common diagnosis. BPPV, vestibular migraine and Meniere's disease had the highest PPVs for accuracy. No strokes misdiagnosed. The Dix-Hallpike manoeuvre and head impulse test were the most commonly performed examinations, though frequently misinterpreted.

Conclusions: Diagnostic accuracy for differentiating central and peripheral aetiologies for dizziness presentations was high. Frequency of bedside testing was suboptimal and increased use may reduce undifferentiated cases. Further research is required to explore better use of bedside testing in improving diagnostic accuracy.

Keywords: Dizziness, Vertigo, Bedside Assessments, Emergency Service, Diagnostic Error

The Role of the Otoliths in Vestibulo-ocular Reflex Adaptation

Khan SI (1,2) and Migliaccio AA (1,2,3)

(1) Balance and Vision Laboratory, Neuroscience Research Australia, Cnr Barker Street & Easy Street, Randwick, Sydney, NSW, 2031, Australia

(2) University of New South Wales, Sydney, NSW, 2033, Australia

(3) Department of Otolaryngology - Head and Neck Surgery, Johns Hopkins University, Baltimore, MD, 21205, USA

The aim of this study was to determine the role of the otoliths in vestibulo-ocular reflex (VOR) adaptation. Until recently the role of the otoliths has been difficult to determine

because there is no surgical or chemical technique that can selectively ablate the otoliths without damaging the semicircular canals. The tilted mouse (Otop 1) lacks functioning otoliths, but has normal semicircular canals, and do not show any permanent phenotype in organ systems other than the otoliths. In 4 Otop 1 mice and 4 control littermates we measured: 1) baseline ocular counter-tilt about the 3 primary axes; 2) baseline horizontal sinusoidal (0.2-10Hz, 20-100°/s) VOR gain (= eye / head velocity); 3) baseline vertical (left-ear-down [LED] and [RED]) sinusoidal VOR; 4) horizontal VOR after gain-increase (x1.5) and gain-decrease (x0.5) adaptation training at 0.5Hz with peak-velocity 20°/s; 5) vertical (left-ear-down and right-ear-down) VOR after gain-increase (x1.5) and gain-decrease (x0.5) adaptation training to one side (LED or RED). Counter-tilt responses in tilted mice were significantly reduced compared to controls, confirming that tilted mice had minimal otolith function. Baseline horizontal and vertical VOR gains were similar between the two mouse types, confirming that the semicircular canals in titled mice were similar to normal. Horizontal VOR adaptation was similar between both mouse types, suggesting that otoliths played a minor role during horizontal VOR adaptation. However, there was a significant difference in vertical VOR adaptation between both mouse types. For the control mouse, adaptation of the VOR gain was most evident when the testing context (LED or RED) was the same as the training context (LED or RED), i.e., they showed context-specific adaptation. Whereas, although the tilted mouse showed the same level of vertical adaptation as the control mouse, context specific adaptation was absent. Our results suggest that context-specific VOR gain adaptation is almost entirely reliant on otolith input and not other contextual cues, e.g., proprioceptive signals.

Mini ear organoids - how do they compare with human vestibular hair cells?

Bryony A. Nayagam¹, Cristiana Mattei¹, Hannah R. Drury², Babak Nasr¹, Rachael Chatterton¹, Tejal Kulkarni¹, Pegah Jamshidi¹, Giovanna D'Abaco¹, Mirella Dottori³, Rebecca Lim²

¹ The University of Melbourne, ² The University of Newcastle ³ The University of Wollongong

Mammalian hair cells exist in relatively low numbers and lose their capacity to regenerate early in development. As such, the derivation of inner ear tissue from human pluripotent stem cells (hPSC) sources offers an opportunity to study human inner ear development and provides a platform for drug screening and disease modelling.

Methods: We employed a dynamic three-dimensional rotary cell culture system for deriving inner ear organoids from H9 human PSCs over a time course of 16 weeks *in vitro*. Analyses of differentiation and mechanosensitivity of hPSCs-derived organoids were performed using a combination of qPCR, immunofluorescent histology and AM-144 staining. High resolution helium microscopy and patch-clamp electrophysiology were employed to compare the anatomical and physiological characteristics of inner ear organoids to the developing human inner ear. K-Gluconate internal solution was used to record whole cell voltage activated

currents from hPSC-derived inner ear organoids in Liebovitz's L15 cell culture media between 13-16 weeks *in vitro*.

Results: Inner ear organoids show temporal expression of key developmental hair cell markers including Pax2, Athoh1, MyosinVIIa and CtBP2 by immunohistology and qPCR. Mechanosensitive progeny took up AM144 and showed outward currents consistent with those observed in developing human type II vestibular hair cells aged between 12-16 weeks gestation. These currents ranged in amplitude from 350pA to 5nA in response to a voltage step to +20mV (n = 8). Like developing human hair cells, some H9 cells also showed evidence of sodium currents. Moreover, striking morphological similarities were detected between inner ear organoids and developing inner ear using helium microscopy.

Conclusion: Here, we describe a novel three-dimensional system for modelling human inner ear development using rotary cell culture. Our preliminary data suggest that this system is capable of generating a population of inner ear hair cells which resemble an early vestibular phenotype.

A case of Many Ears disease

Celene McNeill

Healthy Hearing and Balance Care, Bondi Junction

This case study presentation will illustrate how symptoms of ear fullness, tinnitus and dizziness may mislead the diagnostic process showing the relevance of audiological tests to reach the correct diagnosis.

Personality characteristics of patients with persistent perceptual postural dizziness; a comparison with BPPV

Stuart Mossman^{1,2}, Freya Smith², Saskia Campbell¹, Dalice Sim¹, , Anne Burston², Gordon Purdie¹, Kay Cunningham²
Otago University Medical School¹, Dept Neurology² and, Wellington Hospital, NZ

AIM To develop a questionnaire in distinguishing subjects with PPPV from easily recognisable BPPV.

METHODS Approximately equal numbers of three different groups of patients were studied with postural phobic vertigo (13) according to Brandt criteria¹, benign paroxysmal positional vertigo (14) and non-dizzy neurological controls (13).

We used seven recognised vestibular and psychological questionnaires to obtain psychometrically quantifiable results, in addition to our own set of questions regarded as relevant to patients with PPPV.

1. Beck's Depression Inventory-II (BDI-II)
2. World Health Organisation Quality of Life-BREF version (WHOQOL-BREF)

3. Anxiety Sensitivity Index-36 R (ASI-36-R)
4. Symptom Checklist-90-Revised (SCL-90-R)
5. Holmes-Rahe Life Stress Inventory (LSI)
6. Vestibular Rehabilitation Benefit Questionnaire (VRBQ)
7. Dizziness Handicap Inventory (DHI)
8. Own designed questionnaire- the Situational Dizziness Questionnaire (SDQ)

RESULTS Compared to BPPV and non-dizzy neurological controls, the PPPV group scored higher on psychological self-assessment measures of depression, obsessive compulsive trait, phobic anxiety (SCL-90) and cognitive anxiety (ASI) with poorer score for quality of life (WHOLQOL-BREF) with symptom exacerbation by social situations and visual stimuli. Those symptoms lasted longer, were more frequent and more disruptive to work (SDQ).

DISCUSSION Findings in the PPPV group are consistent with Brandt's diagnostic features which specify anxiety, depression and obsessive compulsive trait as common features of PPV^{1,2}. A greater perceived handicap as a result of their PPPV symptoms, compared to BPPV group, may explain why these patients feel more disabled and less able to work.

A proposed questionnaire for practical use in the clinic to screen such patients is suggested.

1. Brandt T, Huppert D, Dieterich M. Phobic postural vertigo: a first follow-up. *J Neurol* 1994;241:191–195.
2. Brandt T. Phobic postural vertigo. *Neurology*. 1996;46(6):1515–1519.

Suppression of the Vestibular Short Latency Evoked Potential with Electrical Stimulation of the Central Vestibular System.

CJ Pastras¹, IS Curthoys², DJ Brown¹

¹The Meniere's Laboratory, Sydney Medical School, The University of Sydney, Sydney, NSW, 2050, Australia

²Vestibular Research Laboratory, The University of Sydney, School of Psychology, Sydney, NSW, 2050, Australia

Background:

Currently the functional role of the Efferent Vestibular System (EVS) is unknown. The EVS has both fast (10-100ms) and slow (5-20s) kinetics, and is thought to be involved in the modification of peripheral vestibular gain and homeostasis. Electrical stimulation (ES) of the mammalian EVS results in modest increases in background afferent firing, *in vivo*. Although efferent mediated effects on spontaneous vestibular activity have been characterized, the same cannot be said about dynamic vestibular activity. To view the effects of the EVS on peripheral dynamic vestibular function we have monitored the Vestibular short-latency Evoked Potential (VsEP) evoked by Bone-Conducted Vibration (BCV) during electrical stimulation of the EVS in anaesthetized guinea pigs.

Methods:

The VsEP was recorded from a facial nerve canal electrode. A posterior craniotomy was undertaken to expose the floor of the fourth ventricle for EVS stimulation. A bipolar stimulating electrode pair was placed in the area of the EVS cell bodies using stereotaxic map coordinates and functional responses. Cochlear responses following ES at the midline were also recorded as a reliable measure of peripheral efferent activity. After ablating the cochlea, VsEPs were evoked shortly after ES of the EVS, with a variety of stimulation protocols used to characterize the changes.

Results:

ES of the EVS resulted in a suppression of the VsEP in all animals, at a threshold of approximately 80 μ A. The suppression occurred with ES localized to a small region at the ipsilateral floor of the fourth ventricle, lateral of the facial nerve genu and was abolished following electrolytic lesion. VsEP suppression occurred following a single ES pulse, and the level of suppression varied with current strength and shock delay. The VsEP amplitude was suppressed by more than 50% when the delay between the ES and the VsEP was less than 3ms, but there was little suppression with delays greater than 10ms. The VsEP threshold and latency did not change during ES, irrespective of rate or level. Strychnine and DMPP treatment failed to block the VsEP suppression, despite blocking CAP suppression with midline stimulation. Finally, ES produced a nerve response (ECAP) immediately following the ES artefact, whose amplitude correlated closely with the VsEP suppression.

Conclusion

Ultimately, we suggest the observed VsEP suppression results from antidromic stimulation of the afferent neurons, causing neural blockade of the afferent response (VsEP). All other attempts to induce effects using ES in the brainstem failed to produce any changes in the VsEP.

Calcium in balance: GCaMP imaging in the crista ampullaris

HA Holman¹, **LA Poppi**², M Fereck¹ and RD Rabbitt¹

¹Department of Bioengineering, Otolaryngology-Head Neck Surgery, Neuroscience Program, University of Utah, Salt Lake City, UT84112

²School of Biomedical Sciences and Pharmacy, University of Newcastle and Hunter Medical Research Institute, Newcastle, NSW 2308, Australia

Background

ACh is the primary fast neurotransmitter released by vestibular efferent neurons in the inner ear. ACh acts on hair cells and afferents by activating nicotinic and/or muscarinic ACh receptors, in order to modulate sensory activity. This modulation is known to involve significant changes in available intracellular Ca²⁺. We use a new optical approach to measure changes in available intracellular Ca²⁺ in vestibular hair cells and afferents following ACh exposure.

Methods

Transgenic mice used for this study express the fluorescent Ca^{2+} reporter – GCaMP5G – which fluoresces when it bound to a free Ca^{2+} ion. Therefore, as the concentration of available intracellular Ca^{2+} increases, we can measure the changes in fluorescence using a swept-field confocal microscope. Confocal microscopy allows for the imaging of fluorescence changes in a single z plane, and by repeating this through the depth of each cell, the Ca^{2+} responses can be reconstructed in three dimensions. Live cell GCaMP Ca^{2+} images were obtained from a semi-intact preparation of the anterior crista, horizontal crista, and utricle. A pressure-driven, electronically programmed micro-perfusion system was used to deliver ACh, and images were taken from time sequences at each focal depth before, during and after ACh application.

Results

GCaMP5G expression was predominantly in a subset of type I hair cells (type Ig), and a subset of newly identified cells (myosin VIIa-negative) in the peripheral eminentia cruciatum (EC). Low-level GCaMP5G expression was also noted in calyces and neural dendritic fields. GCaMP5G allowed for identification of cells and live Ca^{2+} imaging in response to ACh in all of the aforementioned cell types. ACh-evoked $[\text{Ca}^{2+}]$ modulation was observed in type I hair cells, afferents, and EC cells ($n = 8$ cristae). Type Ig hair cells showed decreased GCaMP fluorescence following ACh application, while calyces enveloping the same cells exhibited an increase in GCaMP fluorescence. The time course of the Ca^{2+} changes in the hair cell/calyx pair was consistent with mAChR activation on the calyx. EC cells exhibited a strong $[\text{Ca}^{2+}]$ evoked response by increased GCaMP fluorescence following ACh application that was blocked by the mAChR antagonist, atropine.

Conclusions

GCaMP responses in a subpopulation of type I hair cells, afferent calyces, afferent dendrites and uniquely identified EC cells from ACh evoked $[\text{Ca}^{2+}]$ transients and the kinetics suggest the involvement of muscarinic acetylcholine receptors, and varied postsynaptic responses in different cell types. This is in keeping with previous work in the field that shows hyperpolarisation in hair cells, and excitation in afferents. Description of muscarinic activity in cells of the EC is novel.

Toward objective clinical diagnosis of cerebellar ataxia

Power L³, Pathirana PN⁴, Dang Nguyen N⁴, My Dung Phan T⁴, Kashyap B⁴, Horne M³, Szmulewicz DJ^{1,2,3}

1. Balance Disorders and Ataxia Service, Royal Victorian Eye and Ear Hospital, Melbourne, Australia
2. Cerebellar Ataxia Clinic, Neuroscience Department, Alfred Health, Melbourne, Australia
3. Florey Institute of Neuroscience and Mental Health, Melbourne, Australia
4. Faculty of Science Engineering and Built Environment, Deakin University, Melbourne, Australia

One of the most common and medically concerning manifestations of ataxia is gait imbalance. In the case of cerebellar ataxia, there are a number of additional coordination functions which may be effected, and

this adds to the disease burden associated with the cerebellar ataxias. There is a lack of 'tools' for readily describing and measuring dysfunction in these systems. This current program of work aims to instrument key aspects of the clinical examination that are utilized in the assessment of the ataxic patient. Customized inertial measurement units, speech recognition and visual-kinematic systems have been applied to a set of functional cerebellar domains.

Vestibular dysfunction is poorly identified in people admitted to sub-acute rehabilitation following an injurious fall.

Ann E Rahmann, PhD^{1,2} and Nancy L. Low Choy, PhD¹

5. School of Physiotherapy, Australian Catholic University, Banyo Campus
6. Community, Indigenous and Subacute Services, Metro North Hospital and Health Service, Queensland Health

Objectives: To determine the prevalence of vestibular dysfunction amongst older adults admitted to sub-acute rehabilitation following an injurious fall.

Study Design: Review of ad-hoc vestibular assessments undertaken over three month period followed by a chart audit of current patients admitted to a 70 bed Queensland Health sub-acute rehabilitation facility.

Methods: Ad-hoc screening of inpatients for vestibular dysfunction occurs in our facility with brief de-identified details of findings collated by physiotherapy staff and reviewed as part of this project. An audit of current inpatient medical charts was then completed over two days to determine the number of vestibular assessments undertaken by physiotherapists and recorded in the chart.

Results: Data from the 12 clinical vestibular assessments undertaken over a 3-month period were collated. 6 out of the 12 patients had been admitted for rehabilitation following a fall. 10 out of the 12 had a vestibular dysfunction identified on clinical physiotherapy assessment. 7 were found to have a peripheral vestibular dysfunction (6 with BPPV) and 3 had mixed peripheral and central vestibular dysfunction identified. The Vestibular Screening Tool (VST) was $>4/8$ (indicating need for vestibular physiotherapy referral) in 7/12 patients. 5 patients scored $<4/8$ on the VST, with 3 of these patients diagnosed with a vestibular dysfunction on clinical assessment.

The subsequent chart audit of 70 current inpatients showed 47% had been admitted with an orthopaedic or musculoskeletal diagnosis following a fall. However only 2 had undergone a physiotherapy vestibular assessment and both were diagnosed and treated for BPPV.

Conclusions:

Older adults admitted to our sub-acute rehabilitation facility following a fall / fracture don't always report dizziness or vertigo and vestibular assessment by physiotherapists is therefore not routine. A significant number of patients are potentially being discharged with an unidentified / untreated vestibular dysfunction. Whether this unidentified vestibular dysfunction is related to the rate of post-discharge falls requires further investigation.

Vertigo in the Emergency Department: new bedside tests

Tamás T. László dr., Garai Tibor dr., Tompos Tamás dr., Szirmai Ágnes dr.

**Petz Aladár Megyei Oktató Kórház, Fül-Orr-Gégészeti és Fej-, Nyaksebészeti Osztály, Győr
Semmelweis Egyetem, Általános Orvostudományi Kar, Fül-Orr-Gégészeti és Fej-Nyaksebészeti
Klinika, Budapest**

According to international statistics, the first examination of 25% of patients with vertigo is carried out in Emergency Departments. The most important task of the examining physician is to diagnose life threatening pathologic processes. One of the most difficult otoneurological diagnostic challenges in Emergency Departments is to differentiate between dangerous posterior scale stroke presenting with isolated vertigo and the benign vestibular neuritis. These two disorders can be safely differentiated using fast, non-invasive, evidence based bedside tests which have been introduced in the past few years. 35% of stroke cases mimicking vestibular neuritis (pseudoneuritis) are misdiagnosed at the Emergency Department, and 40% of these cases develop complications. During the first 48 hours, sensitivity for stroke of the new test that is based on the malfunction of the oculomotor system is better than the diffusion-weighted cranial magnetic resonance imaging. Using special test glasses each component of the new test can be made objective and repeatable.

Patient Presentation....'a puff of hot air'

Pam Reynolds
On Balance Physiotherapy, Hornsby

71yo gentleman presented with sequential episodes of vestibular dysfunction in May 2015 and May 2017.

In 2015 he had one single episode which resolved after minutes and was followed, three months later by a series of episodes lasting up to 5 minutes. Neurologist reported L beating nystagmus and positive R Head Impulse Test. vHIT showed refixation saccades bilaterally for lateral and posterior canals $L > R$. He did not fall on matted Romberg.

In 2017 48 hour acute vestibular episode, unable to walk, unsteady on feet since, able to drive after 4/7 and was back to work. vHIT now shows bilaterally reduced VOR gain $R > L$, both significantly reduced since previous episode. Does not fall on matted Romberg or on 0.5 perturbation with VR on foam.

This presentation is not typical of a unilateral loss and I am hoping to provoke some discussion as to what this presentation represents.

VOR rehabilitation RCT using StableEyes: Preliminary data

Rinaudo C (1,2), Schubert MC (3,4), Cremer PD(4,5), Todd CJ(1), Figtree WVC(1), Mahfuz MM(1,2), Khan SI(1,2) and Migliaccio AA(1,2,7).

(1) Balance and Vision Laboratory, Neuroscience Research Australia, Cnr Barker Street & Easy Street, Randwick, Sydney, NSW, 2031, Australia

(2) University of New South Wales, Sydney, NSW, 2033, Australia

(3) Laboratory of Vestibular NeuroAdaptation, Department of Otolaryngology - Head and Neck Surgery, Johns Hopkins University, Baltimore, MD, 21205, USA

(4) Department of Physical Medicine and Rehabilitation Johns Hopkins University, Baltimore, MD, 21205, USA

(5) Royal North Shore Hospital, St Leonards, NSW, 2065, Australia

(6) University of Sydney, Camperdown, NSW, 2006, Australia

(7) Department of Otolaryngology - Head and Neck Surgery, Johns Hopkins University, Baltimore, MD, 21205, USA

Background:

Conditions affecting the peripheral vestibular system are known to affect the vestibulo-ocular reflex (VOR), with low gain and catch-up saccades. Subsequently, a patient suffers dizziness, poor balance, vision instability and poor quality of life. Despite best efforts from medical intervention after initial presentation and physical therapy for ongoing symptomatology, improvements in the VOR are generally not seen.

Aim:

We developed the unilateral incremental VOR adaptation technique, shown to increase the VOR gain with 15 minutes of training. Patients with peripheral vestibular lesions suffer poor balance and gait, vision instability

during head movement and poor quality of life. Our aim is to determine the short and long-term benefits of daily incremental VOR adaptation training on their VOR, as well as the other makers of vestibular function.

Methods:

A double-blinded placebo-controlled cross-over study is used to determine the benefits of once daily incremental VOR adaptation technique. All subjects have confirmed isolated peripheral vestibular lesions of at least 6 months duration from a Neurologist. The VOR response is measured via video oculography, scleral search coils and dynamic visual acuity (DVA) testing. Balance is measured with computerized posturography, inertial sensors and video capture. Gait is measured with a sensor mat and inertial sensors. Subjective findings are scored with the DHI. Subjects are enrolled in a short-term (1 week) and long-term (18 months) study with monthly reviews of vestibular function.

Results:

15 subjects have participated in the short-term study and 12 of these continued onto the long term study. Three (1 intervention and 2 controls) have progressed passed the initial 6 month arm and are now in the middle of the 6 month wash-out phase. Our preliminary findings (in one indicative subject) show that the intervention yields a gradual 40% increase in VOR response and earlier recruitment of saccades over 6 months, a normalized DVA score (from 0.7 to 0.15 logMAR) and improved quality of life (DHI from 52 to 40). Retention of improvements were seen at a 3 month follow-up (VOR unchanged, DVA 0.3 logMAR, DHI 30). Control subjects also reported feeling better due to the training, but there was no noticeable improvement in our objective measures.

Conclusion:

Preliminary results suggest once daily incremental VOR adaptation does increase the VOR response (gain and saccade characteristics), as well as retain these improvements, in patients with isolated peripheral vestibular hypofunction.

Vestibular projections to the splenius capitis neck muscles in humans

Sally M Rosengren, Konrad P Weber, Danielle L Dennis, Sendhil Govender, Miriam S Welgampola, James G Colebatch

The vestibulo-colic reflex (VCR) in humans is well-defined for only the sternocleidomastoid (SCM) neck muscle. However, other neck muscles also receive input from the balance organs and participate in neck stabilization.

We therefore investigated the sound-evoked VCR projection to the splenius capitis (SC) muscles using 2 ms, 500 Hz tone bursts. We compared surface and single motor unit responses in the SCM and SC muscles in 10 normal volunteers. We also recorded surface responses in patients with vestibular loss but preserved hearing and hearing loss but preserved vestibular function. The strongest single motor unit responses were recorded in the ipsilateral SCM and contralateral SC.

In both cases there was a significant decrease or gap in single motor unit activity: in SCM at 12.7 ms for 51/58 motor units, and in SC at 11.7 ms for 46/66 units. There were fewer significant responses in the contralateral SCM and ipsilateral SC muscles, and they consisted of both increases and decreases in activity. Surface responses in ipsilateral SCM consistently showed a biphasic positive-negative wave, while there were occasional, smaller negative-positive responses on the contralateral side. Surface responses over the ipsilateral SC were inconsistent, while those over the contralateral SC were positive-negative during neck rotation and negative-positive during neck extension. Responses in SC were present in the patients with hearing loss and absent in the patient with vestibular loss, confirming their vestibular origin. An initial decrease in single motor unit activity suggests an inhibitory projection, while an increase indicates an excitatory projection.

The results confirm an uncrossed inhibitory vestibular projection to the ipsilateral SCM and a crossed inhibitory projection to the contralateral SC. This pattern is consistent with the agonist relationship between these muscles.

Cerebellar dizziness and cerebellar ocular motor disorders: diagnosis and current pharmacotherapy

Michael Strupp MD, FRCP, FANA, FEAN, Katharina Feil, MD and Tatiana Bremova, MD, PhD

Department of Neurology, University Hospital, Munich and German Center for Vertigo and Balance Disorders, Hospital of the LMU Munich, Germany

michael.strupp@med.uni-muenchen.de

Background and Summary

The role of cerebellar dysfunction as a cause of dizziness is evidently underestimated. It is often associated with cerebellar ocular motor disorders which can be the key to the diagnosis. Therefore, the first part of the presentation deals with the various cerebellar ocular motor disorders in patients presenting with dizziness based on a recent study on a large cohort.

The pharmacotherapy of cerebellar disorders, cerebellar ataxia and cerebellar nystagmus was assumed to be almost impossible (1). However, three pharmacological agents have been introduced over the last 15 years which show a benefit in certain diseases: **aminopyridines** (potassium channel blockers), **acetyl-DL-leucine** (a modified amino acid) and chlorzoxazone (an activator of small calcium-activated potassium channels). Therefore, the second part gives an overview of their use in various cerebellar disorders ranging from downbeat nystagmus to inherited neurometabolic diseases such as Niemann-Pick type C and gangliosidoses, including translational and back-translational research with animal models.

Cerebellar ocular motor disorders as a key to the diagnosis of dizziness

Cerebellar diseases that are classically known for symptoms like limb ataxia, gait disturbances and dysarthria (2) may also be an important contributing factor to central vertigo syndromes, due to the multiple connections of the cerebellum to the vestibular system. Therefore, the main goal of this study was to identify patients with vertigo caused by different cerebellar diseases.

Methods

The medical records of all patients diagnosed with cerebellar disease in the German Center for Vertigo and Balance Disorders between 2011 and 2015 were reviewed. All patients, who presented in the outpatient clinic and were diagnosed having a cerebellar disease, were included in the final analysis. Their workup comprised a detailed medical history, standardized neurological, neuro-otological and neuro-ophthalmological examinations and further diagnostic procedures, such as MRI findings, posturographic examinations and laboratory tests.

Results

A total of 463 patients (215 men) out of 5400 patients presenting with vertigo or dizziness were included because of cerebellar signs and symptoms. Mean age at time of diagnosis was 65.5 ± 15.6 . Mean symptom duration till diagnosis was 4.9 ± 5.9 SD years. 85.5% ($n=396$) of the patients with the final diagnosis of a cerebellar syndrome suffered from vertigo and/or dizziness. 84.1% reported having permanent dizziness, 31.8% reported having attacks of vertigo and 16.2% reported having both. 46.2% of patients reported a subjective progression of the symptoms over time. 66.5% of patients presented with unsteadiness of gait, 19.4% ($n=90$). Ocular motor disturbances like diplopia, oscillopsia and blurred vision were reported in 37.8% ($n=175$) and speech disturbances in 19.4% ($n=90$). 35.9% of patients had isolated mild to moderate cerebellar ocular motor disturbances without any limb ataxia, dysarthria or other sign of cerebellar ataxia followed by downbeat nystagmus syndrome in 24.2% and cerebellar ataxia in 20.5%; CANVAS was diagnosed in 11.0% of cases (**Fig. 1**). 87.1% of patients had saccadic smooth pursuit and 28.1% strabism (which can also be a cerebellar sign). Saccades, either hyper- or hypometric, were pathological in 42.3%. Finally, 45.1% had a pathological fixation suppression of the VOR. MRI examinations were available in 41% of cases ($n=190$) and considered to be pathological in 106 cases (56 patients with cerebellar atrophy). 269 patients underwent posturography, with all of them having pathological results, with a 3-Hz sway typical of cerebellar vermal dysfunction in 15.6%.

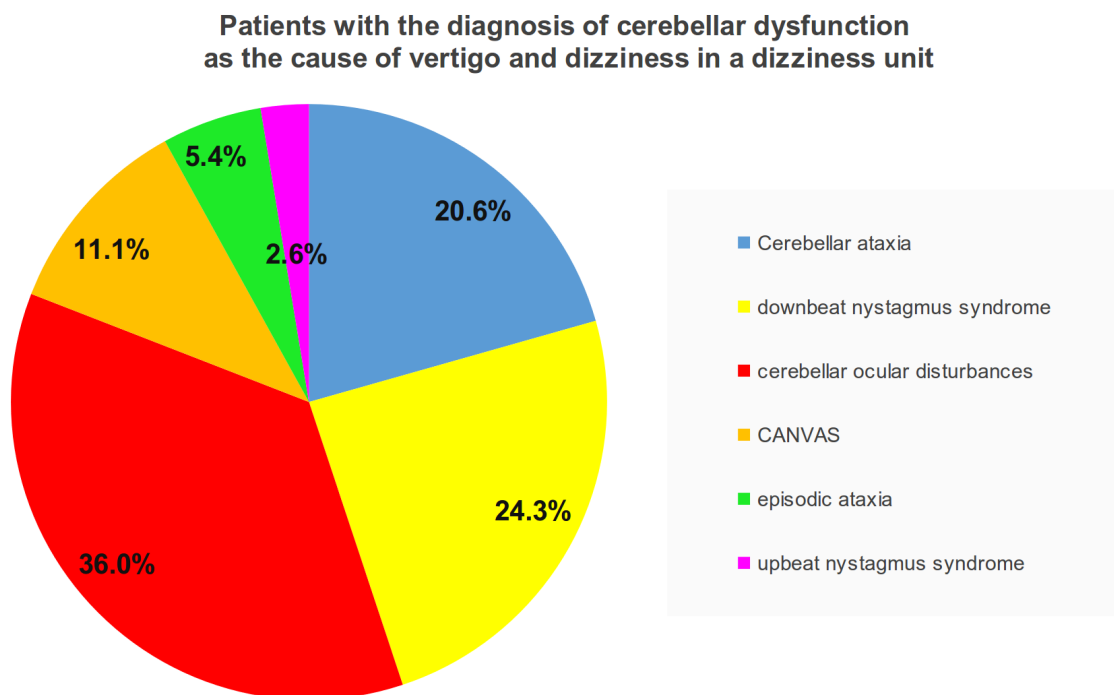


Figure 1. Frequency of different cerebellar dysfunction and syndromes in 463 patients from a total of 5400 consecutive patients in the German Center for Vertigo and Balance Disorders Abbreviations: CANVAS: Cerebellar ataxia, neuropathy, vestibular areflexia syndrome

Conclusions

Dysfunction of the cerebellum is a relatively frequent cause of vertigo and dizziness. One third of the 463 patients with cerebellar vertigo and dizziness had isolated cerebellar ocular motor dysfunction only, one fifth of the patients had downbeat nystagmus syndrome. Therefore, from a clinical point of view, a careful examination of eye movements and nystagmus is often the key to the diagnosis.

Pharmacotherapy of cerebellar ataxias and nystagmus

Aminopyridines

Treatment of different types of nystagmus

Downbeat nystagmus

Downbeat nystagmus (DBN) is a frequent form of acquired persisting fixation nystagmus (3), mostly due to cerebellar degeneration or ischemia leading to a floccular hypofunction (4, 5). Patients with DBN predominantly suffer from postural imbalance and cerebellar gait ataxia, as well as oscillopsia with reduced visual acuity due to a corrective downward saccade following a spontaneous upward drift (for references see (6)).

Already in 2003 it was shown in a randomized-controlled cross-over trial (RCT) that 3,4-DAP had a significant effect on the intensity of DBN (7): a single dosage of 20 mg reduced the mean peak slow-phase velocity from 7.2 deg/s before treatment to 3.1 deg/s 30 min after ingestion. Except for transient perioral or digital paresthesia and nausea and headache the agent was well tolerated. These findings were confirmed by others (8-10). Although 3,4-DAP also improved DBN in patients with spinocerebellar ataxia type 6 (SCA6), there was no improvement of postural control or other ataxic symptoms after one week of treatment with 3,4-DAP (20mg b.i.d.) (8). It evidently works best in patients with cerebellar atrophy without having a significant effect in patients with structural brainstem lesions most likely because the target structure is not intact anymore (11). Recordings with the scleral-coil technique showed that 4-AP restores the function of the vertical and horizontal neural integrator which also explains its effects on gaze-evoked nystagmus (11). Equal doses of 4-AP were superior to 3,4-DAP because 4-AP is more lipid-soluble and crosses the blood-brain-barrier more easily (12) and should, therefore, be preferred (13).

In a more recent RCT it was shown that 4-AP in DBN reduces the slow phase velocity of DBN by about 50% and improves visual acuity at a dosage of 5mg 4-AP q.i.d. (14). Further on, at a higher dosage of 10mg qid a reduction of postural sway and an improvement of motor performance assessed by the timed “get-up-and-go test” was demonstrated. However, the patients did not notice any subjective improvement, probably because of the short half-life of the drug. This shortage may be overcome by the prolonged-release form of 4-AP, FampyraTM, which is - in a dosage of 10-20 mg/d - also efficient (15). Since the latter was only an observational study, further trials with the new formulation are needed.

In conclusion, based on the current state-of-the-art RCTs the use of 4-AP in a dosage of 5 mg two to four times per day is generally recommended for the treatment of DBN (16); the prolonged-release form (10 to 20 mg per day) is also effective (15).

Upbeat nystagmus, central positioning and head-shaking nystagmus

Upbeat nystagmus (UBN) is rarer than DBN and is also a fixation nystagmus. In primary position the UBN beats upward. Oscillopsia is often very irritating, but the symptoms of

UBN are usually transient. In most cases, paramedian lesions in the medulla oblongata or the midbrain are found, i.e. in patients with MS, brainstem ischemia or tumors, or Wernicke's encephalopathy (for references see (17)). In a single case it was demonstrated that the treatment with 10 mg of 4-AP reduced the mean peak slow phase velocity of UBN from 8.6 deg/s to 2.0 deg/s, causing subjective relief from distressing oscillopsia, and impaired upward smooth pursuit was restored (gains: pre 0.38; post 0.86) (18). In the dark, UBN was not affected by 4-AP. Therefore, it was proposed that 4-AP improved the function of cerebellar pathways that mediate gaze-holding and smooth pursuit by intensifying the excitability of cerebellar PCs.

In another so far single case it was found that 4-AP also suppresses central positioning DBN; its mode of action in this type of nystagmus is due to an increased activity of the flocculus and ocular motor vermis - as was demonstrated by an FDG-PET (19) - which inhibits vestibular nuclei neurons.

Finally, 3,4-DAP can also suppress severe head-shaking nystagmus; its mode of action could be an improvement of nerve conduction or an increase of cerebellar inhibitory input (20). Further studies are necessary for all three entities.

Treatment of episodic ataxia type 2

Episodic ataxia type 2 (EA 2) belongs to the growing number of ion channel disorders and is the most frequent subtype of episodic ataxia. In about 60% of patients mutations of the CACNA1A gene, which encodes the alpha-subunit of the P/Q-type calcium channel are found (21, 22). The leading symptoms are recurrent attacks of ataxic symptoms, most often provoked by stress, physical exertion or alcohol, lasting for hours to days. Another important feature is persisting central cerebellar ocular disturbances in between the attacks. More than 90% of patients exhibit central ocular motor disturbances such as gaze-holding deficits, saccadic smooth pursuit, impaired suppression of the vestibulo-ocular reflex and especially DBN (22). These clinical signs also allow EA 2 to be differentiated from migraine with only minor ocular motor dysfunction (23, 24).

In the past, the treatment of choice was the carboanhydrase inhibitor acetazolamide in a dosage of 250 – 1000 mg per day (25). It may act via changes of pH and thereby the transmembrane potential and excitability of neurons due to acidification. From a clinical point of view, there are, however, so far no RCTs on its efficacy. Furthermore, its adverse effects (e.g., kidney stones, nephrocalcinosis, hyperhydrosis, paresthesia, muscle stiffening with easy fatigability, and gastrointestinal disturbances, dose-related) considerably limit its use in clinical practice.

Nowadays the treatment of choice is 4-AP. In 2004 an observational study on three patients demonstrated a reduction of attacks, with the drug being well tolerated (26). In 2011 these findings were confirmed in an RCT on patients with EA 2 and familial ataxias; during treatment QoL also improved (27). The recommended dosage is 5 to 10 mg t.i.d.. The sustained release form of 4-AP [AmpyraTM (Acorda, USA) or FampyraTM (Biogen Idec, Europe)] was also shown to be effective in EA2, too(28). Currently we could also demonstrate in an RCT at the University Hospital Munich, the "EAT-2-TREAT trial" that FampyraTM and acetazolamide are both effective for the treatment of EA2.

As mentioned above, in back-translational research the mode of action of 4-AP was studied in the TM (29, 30), an animal model of EA2; its major effect is evidently by increasing the precision of pace-making of PCs. This, however, is not in agreement with a mathematical model of increased excitability in EA2 (31) and other animal studies of the tottering mouse which suggested an extra-floccular effect (32).

Another possible mode of action comes from a more recent paper also in the TM (33). Although, in EA2 the emphasis has been on cerebellar dysfunction, patients also exhibit episodic, non-motoric abnormalities involving the cerebral cortex. This study demonstrated episodic, low-frequency oscillations (LFOs) throughout the cerebral cortex of TM. The LFOs in TM are mediated in part by neuronal activity. The high-power LFOs are decreased markedly by 4-AP and acetazolamide, the primary treatment options for EA2, suggesting disease relevance. Together, these findings demonstrate that the high-power LFOs in the TM cerebral cortex represent a highly abnormal excitability state that may underlie non-cerebellar symptoms such as seizures that characterize *CACNA1A* mutations (33).

Finally, AP normalizes the firing rate and the motor behavior in ataxin-1 mutant mice in vivo (34). It also has a neuroprotective effect because mice treated early demonstrated better motor function, which may be mediated by an enhanced electrical activity of PCs (34). Therefore, long-term treatment starting early in the course of neurodegenerative ataxias may help to improve the outcome. This may also be true for other cerebellar indications such as EA2, DBN and cerebellar gait ataxia.

Treatment of gait ataxias

Based on the positive effects of AP on cerebellar oculomotor functions there is a rationale to hypothesize on a possible effect of AP on cerebellar locomotion control. In a case description of two patients with progressive cerebellar ataxia due to mutations of the *CACNA1A* gene, 4-AP improved the precision of stepping (the coefficient of variation of stride time); the effect was speed-dependent with the highest magnitude during fast walking (35). This finding was further extended by a retrospective case series with 31 patients with cerebellar gait ataxia due to different etiologies (multisystem degeneration with cerebellar ataxia, sporadic adult-onset ataxia, cerebellar stroke, *CACNA1A* mutations, DBN syndrome; no patients with MS) (36). On an individual basis, 25 patients showed an improvement of gait performance. Treatment with 5mg 4-AP enhanced the preferred walking speed and decreased the coefficient of variation of stride time (both parameters are linked to a better dynamic stability during walking and are associated with a higher risk for falls). The effect of 4-AP on gait was independent of the severity of ataxia as assessed in the Scale for assessment and rating of ataxia (SARA) but was associated with a high magnitude of temporal gait variability prior to treatments. Thus, temporal gait variability might serve as a prognostic factor for the response to 4-AP in cerebellar ataxia.

A randomized, placebo-controlled monocentric study with FampyraTM (FACEG) is currently being performed to further evaluate the effect of sustained release 4-AP on gait stability, walking performance and falls in patients with different forms of ataxia. As mentioned above, 4-AP improves the precision of the intrinsic pacemaker functions of PCs (29). A higher precision of this function might result in a higher regularity of stepping in humans, but this transfer is widely speculative.

A summary of the indications, dosages and precautions is given in table 1 and in a recent review article from which many parts of the above mentioned paragraphs were taken (37).

Indication	Drug	Dosage	Precautions	Further information
DBN	4-AP	5 mg, starting with bid, up-titration up to 20 mg/d possible	Prolonged QTc-time in ECG as a clinically relevant limitation	Monitoring of effect of medication by dynamic VA or SPV in VOG Compassionate use of medication
DBN	4-AP SR	10 mg bid	As given in the medication information	No up-titration needed, one should always keep in mind its contraindications, side effects, and interactions with other drugs Monitoring of effect of medication by dynamic VA or SPV in VOG Compassionate use of medication
Central postioning nystagmus, UBN, central head-shaking nystagmus	4-AP	5 mg, starting with bid, uptitration up to 20 mg/d possible	Prolonged QTc-time in ECG as a clinically relevant limitation	Monitoring of effect of medication by VOG and/or filming of patient's eye movements
Gait ataxia due to cerebellar ataxia of different etiologies	4-AP	5 mg tid	Prolonged QTc-time in ECG as a clinically relevant limitation	Monitoring of effect of medication by 8MW or get-up-and-go test Compassionate use of medication
Gait ataxia due to cerebellar ataxia of different etiologies	4-AP SR	10 mg bid	As given in the medication information	No up-titration needed, one should always keep in mind its contraindications, side effects, and interactions with other drugs Monitoring of effect of medication by 8MW or get-up-and-go test Compassionate use of medication
Gait ataxia due to MS	4-AP SR	10 mg bid	As given in the medication information	No up-titration needed, one should always keep in mind its contraindications, side effects, and interactions with other drugs Monitoring of effect of medication by 8MW or get-up-and-go test
EA2	4-AP	5 mg tid	Prolonged QTc-time in ECG as a clinically relevant limitation	Monitoring of effect of medication by patient's diary (number of attacks) Compassionate use of medication
EA2	4-AP- SR	10 mg bid	As given in the medication information	Monitoring of effect of medication by patient's diary (number of attacks) Compassionate use of medication

Table 1. Indications for aminopyridines for cerebellar disorders

Effects of acetyl-DL-leucine in cerebellar ataxias

Background

Acetyl-DL-leucine (AL) is a modified amino acid which has been used to treat vertigo since 1957. It may act due to its direct effect on neurons, as was shown in the vestibular nuclei. Due to the phylogenetical and electrophysiological similarities and close interactions between vestibular and deep cerebellar neurons, we had hypothesized that there may also be a positive effect on ataxic symptoms in cerebellar disorders.

Results

In 2013, in a first case series on 13 patients with different types of cerebellar ataxia we showed that AL (5 g/ day for 1 week) significantly improved the symptoms in terms of SARA, SCAFI and Qo (38). Mean total SARA (\pm SD) decreased from a baseline of 16.1 ± 7.1 to 12.8 ± 6.8 on medication ($p = 0.002$). There were also significant improvements in sub-scores for gait, speech, finger-chase, nose-finger-test, rapid alternating movements and heel-to-shin. Furthermore, patients showed a significantly better performance in the SCAFI consisting of the 8-m-walking-time, 9HPTD and the PATA rate. QoL increased during treatment ($p = 0.003$). No side effects were reported. (Videos: www.dgn.org)).

In 2015 we reported in a case series on 12 patients with Niemann-Pick type C (NPC) that AL (5 g per day for one month with a one-month titration) significantly improved the clinical symptoms, measured by SARA, SCAFI, modified disability rating scale (mDRS) and EQ-5D-5L Quality of Life (39). The total SARA-score changed significantly from a baseline of 10.8 ± 11.2 to 7.0 ± 10.7 after one month on medication and 10.5 ± 11.5 post 1 month of washout, indicating an improvement of cerebellar signs on medication ($p = 0.000412$). The total mDRS score was 10.0 ± 5.35 at baseline, 9.0 ± 5.3 , on medication and 10.0 ± 5.4 after one month of washout. The 9HPTD changed significantly on medication. In terms of QoL, the visual analog scale of EQ-5D-5L also changed significantly on medication (videos: www.neurology.org).

A third case series demonstrated an improved so-called coefficient of variation of stride time in the gait analysis of 14 patients with cerebellar ataxia during a treatment with AL (40). The improvement of variability was restricted to the condition of slow walking, where walking stability is thought to critically rely on the sensory integration function of the cerebellum. It should be mentioned that in another case series with 10 patients with degenerative cerebellar ataxia, no improvement in SARA was observed (41). However, 7 out of 10 patients described a subjective improvement on medication.

Conclusions and limitations

Acetyl-DL-leucine significantly improved ataxic symptoms without side effects and therefore showed a good risk-benefit profile. The added value of the above-mentioned case series is the demonstrated safety and tolerability of the agent in various medical conditions with the common symptom of cerebellar ataxia. The obvious limitations of these studies are a) the lack of reference agent (placebo), b) the non-blinded design, and c) the small sample size.

COI

M. Strupp is Joint Chief Editor of the Journal of Neurology, Editor in Chief of Frontiers of Neuro-otology and Section Editor of F1000. He has received speaker's honoraria from Abbott, Actelion, Auris Medical, Biogen, Eisai, GSK, Henning Pharma, Interacoustics, MSD, Otometrics, Pierre-Fabre, TEVA, UCB. He acts as a consultant for Abbott, Actelion, AurisMedical, Heel, IntraBio and Sensorion.

Reference List

- (1) Ilg W, Bastian AJ, Boesch S, et al. Consensus paper: management of degenerative cerebellar disorders. *Cerebellum* 2014 Apr;13:248-268.
- (2) Bodranghien F, Bastian A, Casali C, et al. Consensus Paper: Revisiting the Symptoms and Signs of Cerebellar Syndrome. *Cerebellum* 2015 Jun 24.
- (3) Wagner JN, Glaser M, Brandt T, Strupp M. Downbeat nystagmus: aetiology and comorbidity in 117 patients. *J Neurol Neurosurg Psychiatry* 2008 Jun;79:672-677.
- (4) Zee DS, Yamazaki N, Butler PHZ, Bücker F. Effects of ablation of flocculus and paraflocculus on eye movements in primate. *J Neurophysiol* 1981;46:878-899.
- (5) Kalla R, Deutschlander A, Hufner K, et al. Detection of floccular hypometabolism in downbeat nystagmus by fMRI. *Neurology* 2006 Jan 24;66:281-283.
- (6) Leigh RJ, Zee D. The neurology of eye movements, 5 ed. Oxford, New York: Oxford University Press, 2015.
- (7) Strupp M, Schuler O, Krafczyk S, et al. Treatment of downbeat nystagmus with 3,4-diaminopyridine: a placebo-controlled study. *Neurology* 2003 Jul 22;61:165-170.
- (8) Tsunemi T, Ishikawa K, Tsukui K, Sumi T, Kitamura K, Mizusawa H. The effect of 3,4-diaminopyridine on the patients with hereditary pure cerebellar ataxia. *J Neurol Sci* 2010 May 15;292:81-84.
- (9) Sprenger A, Zils E, Rambold H, Sander T, Helmchen C. Effect of 3,4-diaminopyridine on the postural control in patients with downbeat nystagmus. *Ann N Y Acad Sci* 2005 Apr;1039:395-403.
- (10) Helmchen C, Gottschalk S, Sander T, Trillenber P, Rambold H, Sprenger A. Beneficial effects of 3,4-diaminopyridine on positioning downbeat nystagmus in a circumscribed uvulo-nodular lesion. *J Neurol* 2007 Aug;254:1126-1128.
- (11) Kalla R, Glasauer S, Buttner U, Brandt T, Strupp M. 4-aminopyridine restores vertical and horizontal neural integrator function in downbeat nystagmus. *Brain* 2007 Sep;130:2441-2451.
- (12) Judge SI, Bever CT, Jr. Potassium channel blockers in multiple sclerosis: neuronal Kv channels and effects of symptomatic treatment. *Pharmacol Ther* 2006 Jul;111:224-259.
- (13) Kalla R, Spiegel R, Claassen J, et al. Comparison of 10-mg doses of 4-aminopyridine and 3,4-diaminopyridine for the treatment of downbeat nystagmus. *J Neuroophthalmol* 2011 Dec;31:320-325.
- (14) Claassen J, Spiegel R, Kalla R, et al. A randomised double-blind, cross-over trial of 4-aminopyridine for downbeat nystagmus--effects on slowphase eye velocity, postural stability, locomotion and symptoms. *J Neurol Neurosurg Psychiatry* 2013 Dec;84:1392-1399.
- (15) Claassen J, Feil K, Bardins S, et al. Dalfampridine in patients with downbeat nystagmus--an observational study. *J Neurol* 2013 Aug;260:1992-1996.
- (16) Ilg W, Bastian AJ, Boesch S, et al. Consensus paper: management of degenerative cerebellar disorders. *Cerebellum* 2014 Apr;13:248-268.
- (17) Leigh RJ, Zee D. The neurology of eye movements, 4 ed. Oxford, New York: Oxford University Press, 2006.
- (18) Glasauer S, Kalla R, Buttner U, Strupp M, Brandt T. 4-aminopyridine restores visual ocular motor function in upbeat nystagmus. *J Neurol Neurosurg Psychiatry* 2005 Mar;76:451-453.
- (19) Kremmyda O, Zwergal A, la FC, Brandt T, Jahn K, Strupp M. 4-Aminopyridine suppresses positional nystagmus caused by cerebellar vermis lesion. *J Neurol* 2013 Jan;260:321-323.
- (20) Strupp M, Querner V, Eggert T, Brandt T. Potassium channel blocker 3,4-diaminopyridine improves severe head-shaking nystagmus. *J Vestib Res* 2002;11:263. Abstract
- (21) Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca²⁺ channel gene CACNL1A4. *Cell* 1996 Nov 1;87:543-552.
- (22) Jen JC. Hereditary episodic ataxias. *Ann N Y Acad Sci* 2008 Oct;1142:250-253.
- (23) Strupp M, Zwergal A, Brandt T. Episodic ataxia type 2. *Neurotherapeutics* 2007 Apr;4:267-273.

- (24) Jen JC, Baloh RW. Familial episodic ataxia: a model for migrainous vertigo. *Ann N Y Acad Sci* 2009 May;1164:252-256.
- (25) Jen J, Kim GW, Baloh RW. Clinical spectrum of episodic ataxia type 2. *Neurology* 2004 Jan 13;62:17-22.
- (26) Strupp M, Kalla R, Dichgans M, Freilinger T, Glasauer S, Brandt T. Treatment of episodic ataxia type 2 with the potassium channel blocker 4-aminopyridine. *Neurology* 2004 May 11;62:1623-1625.
- (27) Strupp M, Kalla R, Claassen J, et al. A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias. *Neurology* 2011 Jul 19;77:269-275.
- (28) Claassen J, Teufel J, Kalla R, Spiegel R, Strupp M. Effects of dalfampridine on attacks in patients with episodic ataxia type 2: an observational study. *J Neurol* 2013 Feb;260:668-669.
- (29) Alvina K, Khodakhah K. The therapeutic mode of action of 4-aminopyridine in cerebellar ataxia. *J Neurosci* 2010 May 26;30:7258-7268.
- (30) Weisz CJ, Raike RS, Soria-Jasso LE, Hess EJ. Potassium channel blockers inhibit the triggers of attacks in the calcium channel mouse mutant tottering. *J Neurosci* 2005 Apr 20;25:4141-4145.
- (31) Glasauer S, Rössert C, Strupp M. The role of regularity and synchrony of cerebellar Purkinje cells for pathological nystagmus and episodic ataxia type 2. *Ann NY Acad Sci*. In press 2011.
- (32) Stahl JS, Thumser ZC. 4-aminopyridine does not enhance flocculus function in tottering, a mouse model of vestibulocerebellar dysfunction and ataxia. *PLoS One* 2013;8:e57895.
- (33) Cramer SW, Popa LS, Carter RE, Chen G, Ebner TJ. Abnormal excitability and episodic low-frequency oscillations in the cerebral cortex of the tottering mouse. *J Neurosci* 2015 Apr 8;35:5664-5679.
- (34) Hourez R, Servais L, Orduz D, et al. Aminopyridines correct early dysfunction and delay neurodegeneration in a mouse model of spinocerebellar ataxia type 1. *J Neurosci* 2011 Aug 17;31:11795-11807.
- (35) Schniepp R, Wuehr M, Ackl N, et al. 4-aminopyridine improves gait variability in cerebellar ataxia due to CACNA 1A mutation. *J Neurol* 2011 Sep;258:1708-1711.
- (36) Schniepp R, Wuehr M, Neuhaeusser M, et al. 4-aminopyridine and cerebellar gait: a retrospective case series. *J Neurol* 2012 Nov;259:2491-2493.
- (37) Strupp M, Teufel J, Zwergal A, Schniepp R, Khodakhah K, Feil K. Aminopyridines for the treatment of neurologic disorders. *Neurology: Clinical Practice* 2017;7:65-76.
- (38) Strupp M, Teufel J, Habs M, et al. Effects of acetyl-DL-leucine in patients with cerebellar ataxia: a case series. *J Neurol* 2013 Oct;260:2556-2561.
- (39) Bremova T, Malinova V, Amraoui Y, et al. Acetyl-dl-leucine in Niemann-Pick type C: A case series. *Neurology* 2015 Oct 20;85:1368-1375.
- (40) Schniepp R, Strupp M, Wuehr M, et al. Acetyl-DL-leucine improves gait variability in patients with cerebellar ataxia-a case series. *Cerebellum Ataxias* 2016;3:8.
- (41) Pelz JO, Fricke C, Saur D, Classen J. Failure to confirm benefit of acetyl-DL-leucine in degenerative cerebellar ataxia: a case series. *J Neurol* 2015 May;262:1373-1375.

Peripheral vestibular disorders: a quick update

Michael Strupp MD, FRCP, FANA, FEAN

Department of Neurology, University Hospital, Munich and German Center for Vertigo and Balance Disorders, Hospital of the LMU Munich, Germany
michael.strupp@med.uni-muenchen.de

Purpose

To give a brief update on the five most frequent peripheral vestibular disorders - benign paroxysmal positional vertigo (BPPV), Menière's disease, "acute unilateral peripheral vestibulopathy" (AUVP), previously called vestibular neuritis), vestibular paroxysmia and bilateral vestibulopathy (BVP) - in particular on the new diagnostic criteria according to the International Classification Committee of the Bárány Society and the current treatment.

Benign paroxysmal positional vertigo

Diagnosis

In 2015 the diagnostic criteria for BPPV were published (1). They are as follows:

Canalolithiasis of the posterior canal (pc-BPPV)

7. Recurrent attacks of positional vertigo or positional dizziness, provoked by lying down or turning over in the supine position.
8. Duration of attacks < 1 min.
9. Positional nystagmus elicited after a latency of one or a few seconds by the Dix-Hallpike maneuver or side-lying maneuver (Sémont diagnostic maneuver). The nystagmus is a combination of torsional nystagmus with the upper pole of the eyes beating toward the lower ear and vertical nystagmus beating upward (toward the forehead) typically lasting < 1 minute.
10. Not attributable to another disorder.

Canalolithiasis of the horizontal canal (hc-BPPV)

- A. Recurrent attacks of positional vertigo or positional dizziness provoked by lying down or turning over in the supine position.
- B. Duration of attacks < 1 min.
- C. Positional nystagmus elicited after a brief latency or no latency by the supine roll test, beating horizontally toward the undermost ear with the head turned to either side (geotropic direction changing nystagmus) and lasting < 1 min.
- D. Not attributable to another disorder.

Cupulolithiasis of the horizontal canal (hc-BPPV)

1. Recurrent attacks of positional vertigo or positional dizziness provoked by lying down or turning over in the supine position.
2. Positional nystagmus elicited after a brief latency or no latency by the supine roll test, beating horizontally toward the uppermost ear with the head turned to either side (apogeotropic direction changing nystagmus), and lasting > 1 minute.
3. Not attributable to another disorder.

Pathophysiology and treatment

There is increasing evidence that vitamin D deficiency is a risk factor for BPPV and that its substitution has a benefit (2-6). This is currently being evaluated in an ongoing randomized controlled study of the effect of the substitution of vitamin D on the recurrence rate of BPPV.

With an *in vitro* study with a semicircular canal model (7) the determinants for a successful Sémont maneuver (SM) were analyzed, in particular the effect of time between the movements/steps, angle of body movements as well as the angular velocity of the maneuvers to improve the efficacy of the SM (8). Otoconia trajectories were captured by a video camera. The effects of time between the movements, angles of motion (0°, 10°, 20°, and 30° below the horizontal line), different angular velocities (90, 135, 180°/s), and otoconia size (36 and 50 µm) on the final position of the otoconia in the SCC were tested. The major findings were as follows: Without extension of the movements beyond the horizontal, the *in vitro* experiments (with particles corresponding to 50 µm diameter) did not yield successful canalith repositioning. If the movements were extended by 20° beyond the horizontal position, SM were successful with resting times of at least 16 s. For larger extension angles, the required time decreased. However, for smaller particles (36 µm), the required time doubled. The angular maneuver velocity (tested between 90 and 180°/s) did not have a major impact on the final position of the otoconia.

The two primary determinants for success of the SM are the time between the movements and the extension of the movements beyond the horizontal. The time between the movements should be at least 45 s. Angles of 20° or more below the horizontal line (so-called *Sémont plus*) should increase the success rate of SM.

Based on these results, there is currently an ongoing multi-national study to compare the effects of the SM with the Sémont plus with an overextension of the head by 30°.

Menière's disease (MD)

Diagnosis

In 2015 the new diagnostic criteria for (MD) were published (9):

Meniere's disease

- A. Two or more spontaneous episodes of vertigo, each lasting 20 minutes to 12 hours.
- B. Audiometrically documented low- to medium-frequency sensorineural hearing loss (> 30 dB) in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo.
- C. Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear.
- D. Not better accounted for by another diagnosis.

Probable Menière's disease

- A. Two or more episodes of vertigo or dizziness, each lasting 20 minutes to 24 hours.
- B. Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear.
- D. Not better accounted for by another vestibular diagnosis.

Treatment

The following six measures are **not** effective for the treatment of MD:

- 1) Low-dose treatment with betahistine (16 mg tid versus 48 mg tid versus placebo BEMED trial) (10). This is mainly due to the 99% first-pass effect of betahistine, metabolized by monoamine oxidase B (MAO B) in the gastrointestinal tract and liver. Therefore, the author suggests
 - a. much higher dosages of betahistine (up to 1920 mg per day) or
 - b. the combination of 48 mg tid with the MAO B inhibitor Selegiline (5 mg per day) (11)

- c. in the future, the use of an intranasal spray, bypassing the first-pass effect, reaching blood concentrations 70 times higher than when given orally. This method of application is going to be examined in an RCT in MD.
- 1. The mode of action of betahistine is probably due to an increase of inner ear blood flow (12-15) as an inverse-agonist on the H3 heteroreceptor and/or a direct effect of the H1 receptor in the membrane of the endolymphatic sac, which was also found in the human inner ear (16)
- 2) Endolymphatic sac operation (17)
- 3) Salt-free diet (no state-of-the-art clinical trial)
- 4) Diuretics (18)
- 5) Meniett device (19)
- 6) Intratympanic dexamethasone (otonomy press release, 30.8.2017). In this study a really high concentration of a corticosteroid could be applied to the inner ear. Based on this state-of-the art randomized controlled trial, one can conclude that corticosteroids are not effective at all in MD.

Acute unilateral peripheral vestibulopathy (previously also called vestibular neuritis)

Diagnosis

The recommended new term is “acute unilateral peripheral vestibulopathy” (AUPV) which is preferred over vestibular neuritis because it is likely that it is not always caused by a “neuritis”. The new criteria are currently being elaborated and have not been published yet.

Treatment

There is good evidence for the efficacy of vestibular exercises in AUPV (20). Although effective in various animal models, in a state-of-the art RCT betahistine (48 mg tid versus placebo) did not have an effect on vestibular compensation. The reason is evidently the same as for the negative trials in MD: the oral dosage is much too low.

Bilateral vestibulopathy (BVP)

Diagnosis

According to the current criteria the diagnosis is defined as follows (21):

Bilateral vestibulopathy

A. Chronic vestibular syndrome with the following symptoms

- 1. Unsteadiness when walking or standing plus at least one of 2 or 3
- 2. Movement-induced blurred vision or oscillopsia during walking or quick head/body movements
- 3. Worsening of unsteadiness in darkness and/or on uneven ground

B. No symptoms while sitting or lying down under static conditions

C. Bilaterally reduced or absent angular VOR function documented by bilaterally pathological horizontal angular VOR gain <0.6 , measured by the video-HIT or scleral-coil technique and/or reduced caloric response (sum of bithermal max. peak SPV on each side <6 deg /sec) and/or reduced horizontal angular VOR gain <0.1 upon sinusoidal stimulation on a rotatory chair (0.1 Hz, $V_{max} = 50-162$ deg/sec) and a phase lead >68 degrees (time constant <5 sec).

D. Not better accounted for by another disease

Probable BVP

A. Chronic vestibular syndrome with the following symptoms

- 1. Unsteadiness when walking or standing plus at least one of 2 or 3
- 2. Movement-induced blurred vision or oscillopsia during walking or quick head/body movements
- 3. Worsening of unsteadiness in darkness and/or on uneven ground

B. No symptoms while sitting or lying down under static conditions

C. Bilaterally pathological horizontal bedside head impulse test

D. Not better accounted for by another disease

Treatment

A major breakthrough in the treatment of VP has been the development of the vestibular implant which can restore the function of the VOR and normalize dynamic visual acuity (22-24). It is likely that this device will become commercially available within 5 years.

Vestibular paroxysmia

Diagnosis

The current diagnostic criteria are as follows (25):

Vestibular paroxysmia (each point needs to be fulfilled)

- A) At least ten attacks of spontaneous spinning or non-spinning vertigo
- B) Duration less than 1 minute
- C) Stereotyped phenomenology in a particular patient
- D) Response to a treatment with carbamazepine/oxcarbazepine
- E) Not better accounted for by another diagnosis.

Probable vestibular paroxysmia (each point needs to be fulfilled)

- A) At least five attacks of spinning or non-spinning vertigo
- B) Duration less than 5 minutes
- C) Spontaneous occurrence or provoked by certain head-movements
- D) Stereotyped phenomenology in a particular patient
- E) Not better accounted for by another diagnosis.

Treatment

A recent study showed that oxcarbazepine (600 to 900 mg per day) has a significant effect on the number of attacks (Bremova et al., in press). The other studies published so far are only case series (for review see (26))

Reference List

- (1) von Brevern M, Bertholon P, Brandt T, et al. Benign paroxysmal positional vertigo: Diagnostic criteria. *J Vestib Res* 2015;25:105-117.
- (2) Jeong SH, Kim JS, Shin JW, et al. Decreased serum vitamin D in idiopathic benign paroxysmal positional vertigo. *J Neurol* 2013 Mar;260:832-838.
- (3) Whitman GT, Baloh RW. Seasonality of benign paroxysmal positional vertigo. *JAMA Otolaryngol Head Neck Surg* 2015 Feb;141:188-189.
- (4) Talaat HS, Abuhadied G, Talaat AS, Abdelaal MS. Low bone mineral density and vitamin D deficiency in patients with benign positional paroxysmal vertigo. *Eur Arch Otorhinolaryngol* 2015 Sep;272:2249-2253.
- (5) Talaat HS, Kabel AM, Khaliel LH, Abuhadied G, El-Naga HA, Talaat AS. Reduction of recurrence rate of benign paroxysmal positional vertigo by treatment of severe vitamin D deficiency. *Auris Nasus Larynx* 2016 Jun;43:237-241.
- (6) Sheikhzadeh M, Lotfi Y, Mousavi A, Heidari B, Bakhshi E. The effect of serum vitamin D normalization in preventing recurrences of benign paroxysmal positional vertigo: A case-control study. *Caspian J Intern Med* 2016;7:173-177.
- (7) Obrist D, Hegemann S, Kronenberg D, Hauselmann O, Rosgen T. In vitro model of a semicircular canal: design and validation of the model and its use for the study of canalithiasis. *J Biomech* 2010 Apr 19;43:1208-1214.
- (8) Obrist D, Nienhaus A, Zamaro E, Kalla R, Mantokoudis G, Strupp M. Determinants for a Successful Semont Maneuver: An In vitro Study with a Semicircular Canal Model. *Front Neurol* 2016;7:150.
- (9) Lopez-Escamez JA, Carey J, Chung WH, et al. Diagnostic criteria for Meniere's disease. *J Vestib Res* 2015 Jan 1;25:1-7.

- (10) Adrion C, Fischer CS, Wagner J, Gurkov R, Mansmann U, Strupp M. Efficacy and safety of betahistine treatment in patients with Meniere's disease: primary results of a long term, multicentre, double blind, randomised, placebo controlled, dose defining trial (BEMED trial). *BMJ* 2016;352:h6816.
- (11) Strupp M, Kraus L, Schautzer F, Rujescu D. Menière's disease: combined pharmacotherapy with betahistine and the MAO B inhibitor selegiline – an observational study. *J Vestib Res*. In press 2017.
- (12) Ihler F, Bertlich M, Sharaf K, Strieth S, Strupp M, Canis M. Betahistine exerts a dose-dependent effect on cochlear stria vascularis blood flow in Guinea pigs in vivo. *PLoS One* 2012;7:e39086.
- (13) Bertlich M, Ihler F, Sharaf K, Weiss BG, Strupp M, Canis M. Betahistine metabolites, Aminoethylpyridine, and Hydroxyethylpyridine increase cochlear blood flow in guinea pigs in vivo. *INT J AUDIOL* 2014 Oct;53:753-759.
- (14) Bertlich M, Ihler F, Freytag S, Weiss BG, Strupp M, Canis M. Histaminergic H-Heteroreceptors as a Potential Mediator of Betahistine-Induced Increase in Cochlear Blood Flow. *Audiol Neurotol* 2015 Jun 27;20:283-293.
- (15) Bertlich M, Ihler F, Weiss BG, et al. Role of capillary pericytes and precapillary arterioles in the vascular mechanism of betahistine in a guinea pig inner ear model. *Life Sci* 2017 Aug 14.
- (16) Moller MN, Kirkeby S, Vikesa J, Nielsen FC, Caye-Thomasen P. Expression of histamine receptors in the human endolymphatic sac: the molecular rationale for betahistine use in Menieres disease. *Eur Arch Otorhinolaryngol* 2016 Jul;273:1705-1710.
- (17) Pullens B, Verschuur HP, van Benthem PP. Surgery for Meniere's disease. *Cochrane Database Syst Rev* 2013;2:CD005395.
- (18) Thirlwall AS, Kundu S. Diuretics for Meniere's disease or syndrome. *Cochrane Database Syst Rev* 2006;3:CD003599.
- (19) Russo FY, Nguyen Y, De SD, et al. Meniett device in meniere disease: Randomized, double-blind, placebo-controlled multicenter trial. *Laryngoscope* 2017 Feb;127:470-475.
- (20) Hillier S, McDonnell M. Is vestibular rehabilitation effective in improving dizziness and function after unilateral peripheral vestibular hypofunction? An abridged version of a Cochrane review. *Eur J Phys Rehabil Med* 2016 Jul 12.
- (21) Strupp M, Kim JS, Murofushi T, et al. Bilateral Vestibulopathy: diagnostic criteria. *J Vestib Res*. In press 2017.
- (22) Perez FA, Cavuscens S, Ranieri M, et al. The vestibular implant: A probe in orbit around the human balance system. *J Vestib Res* 2017;27:51-61.
- (23) Guinand N, van de Berg R, Cavuscens S, et al. Restoring Visual Acuity in Dynamic Conditions with a Vestibular Implant. *Front Neurosci* 2016;10:577.
- (24) Valentin NS, Hageman KN, Dai C, Della Santina CC, Fridman GY. Development of a multichannel vestibular prosthesis prototype by modification of a commercially available cochlear implant. *IEEE Trans Neural Syst Rehabil Eng* 2013 Sep;21:830-839.
- (25) Strupp M, Lopez-Escamez JA, Kim JS, et al. Vestibular paroxysmia: diagnostic criteria. *J Vestib Res* 2016;26:409-415.
- (26) Strupp M, Dieterich M, Brandt T, Feil K. Therapy of Vestibular Paroxysmia, Superior Oblique Myokymia, and Ocular Neuromyotonia. *Curr Treat Options Neurol* 2016 Jul;18:34.

Improving the Specificity of VEMP testing in SSCD: Trial by oVEMP

Taylor RL^{1,3,4}, Young AS^{1,2}, Argat E², Fratturo L², Pogson JP¹, Welgampola MS^{1,2}.

1. *University of Sydney, Central Clinical School, Royal Prince Alfred Hospital*
2. *The Balance Clinic and Laboratory, Sydney*
3. *New Zealand Dizziness and Balance Centre*
4. *Whangarei Hospital, New Zealand*

Background: The recording of oVEMP amplitudes to air-conducted (AC) sound is a sensitive screening test for Superior semicircular canal dehiscence (SSCD). However, not all patients with large AC oVEMPs have SSCD on CT imaging. In this study, we reviewed the clinical records and BC oVEMP results of patients who underwent CT imaging investigations for augmented AC oVEMP amplitudes. The study sought to identify alternate diagnoses, also producing large oVEMP responses, and investigated oVEMP outcome measures that would help differentiate between these cases and SSCD.

Methods: Fifty two ears with AC oVEMP amplitudes falling outside normal limits were included in the study. Inclusion criteria required that patients were tested with click AC oVEMPs and BC oVEMPs to two different stimuli (1 ms square-wave pulse and 8 ms 125 Hz sine wave), and had undergone high resolution CT imaging, interpreted by an independent radiologist who was blinded to the VEMP results. True and false positive oVEMP results were determined by comparison with a sample of 21 controls (42 ears) without vestibular symptoms. Receiver Operating Characteristic (ROC) analysis was used to determine the diagnostic efficacy of oVEMP amplitude and latency outcome measures.

Results: Thirty one ears were identified as having SSCD; 21 had alternate diagnoses that included thinning of the bone covering (Near Dehiscence), Vestibular Migraine, Large Vestibular Aqueduct Syndrome and Ménière's disease. BC oVEMP amplitudes to 1 ms pulses and 125 Hz sine waves were not helpful in discriminating between SSCD and non SSCD patient ears ($p>0.05$). In contrast, oVEMP latencies to both BC stimuli were powerful discriminators ($p<0.001$), with a specificity of 100% when using the mean +2 SD of the control group as the cut-off. Sensitivity of the 125 Hz stimulus was higher than for the 1 ms pulse.

Conclusions: A two-step protocol that includes AC oVEMP amplitudes and low frequency BC oVEMP latencies is recommended for optimizing the sensitivity and specificity of VEMP testing in SSCD.

A new measure of vestibulo-cerebellar function?: the vestibulo-cerebellar evoked potential (VCEP)

Neil PM Todd¹ and James G Colebatch²

¹Department of Psychology, University of Exeter, UK; and ²Prince of Wales Clinical School, UNSW, Sydney, Australia.

Over the last decade or so, in addition to the development of vestibular evoked myogenic potentials (VEMPs), we have been interested to investigate central vestibular projections by tracing evoked central responses to the same acoustic and inertial activations of the vestibular end-organs which produce VEMPs (Todd et al 2003, 2008, 2014, 2016, 2017). Of particular interest has been the repeated observation of deep brain sources which are co-active with both the ocular and cervical VEMPs, but especially the OVEMP. In several independent studies the use of brain electrical source analysis (BESA) has indicated that an important location for the origin of the deep sources is the cerebellum. These sources manifest on the surface as well-defined potentials in contralateral parietal-occipital (PO) and neck (CB) leads coincident with n10/p17 OVEMP related potentials in infraocular (IO) leads. At especially PO7/8 and modified CB1/2 leads these are measured as p10/n17 and n10/p17 potentials respectively.

We have recently shown that the PO p10/n17 and CB n10/p17 potentials are highly correlated with the OVEMP related IO n10/p17 across individuals but are dissociated in their modulation by eye gaze and head posture (Todd et al 2017). Whereas the IO n10/p17 is maximal with up-gaze and is not modulated by head posture, the PO p10/n17 and CB n10/p17 potentials are maximal with neutral gaze and are also modulated by head posture, with the maximal response also obtained in a neutral head posture. Also unlike the OVEMP related IO n10/p17, the PO p10/n17 and CB n10/p17 tend to be highly lateralised, mostly to the left –hemisphere (with right ear stimulation). These properties and their common BESA locations have led us to suggest that the PO p10/n17 and CB n10/p17 (two ends of the same dipole) are a manifestation of inhibitory Purkinje cell activity in the contralateral cerebellum associated with gain control of the VOR pathways co-activated with the OVEMP. For these reasons we provisionally refer to the above as vestibulo-cerebellar evoked potentials (or VCEPs). In order to develop the potential clinical use of the putative VCEP, should its cerebellar origin be confirmed, we have explored the use of a simplified montage which may be employed in parallel with the OVEMP and CVEMP montages with electrodes located near PO7/8 referred to the ear lobe A1/2. Early measurements taken with such pairs replicate the above properties, thus confirming the potential viability of a VCEP montage. Further experiments will be required however, both to confirm its cerebellar origin and to demonstrate its clinical value.

Todd NPM, Rosengren SM, Colebatch JG. (2003). A short latency vestibular evoked potential (VsEP) produced by bone-conducted acoustic stimulation. *J Acoust Soc Am* **114**, 3264-3272.

Todd NPM, Rosengren SM, Colebatch JG. (2008). A source analysis of short-latency vestibular evoked potentials produced by air- and bone-conducted sound. *Clin Neurophysiol* **119**, 1881-1894.

Todd NPM, Paillard AC, Kluk K, Whittle E, Colebatch JG. (2014). Source analysis of short and long latency vestibular-evoked potentials (VsEPs) produced by left versus right ear air-conducted 500 Hz tone-pips. *Hear Res* **312**, 91 – 102.

Todd NPM, Govender S, Colebatch JG (2016). Vestibular-dependent inter-stimulus interval effects on sound evoked potentials of central origin. *Hear Res* **341**, 190 – 201.

Todd NPM, Govender S, Colebatch JG (2017). The inion response revisited: evidence for a possible cerebellar contribution to vestibular-evoked potentials produced by air-conducted sound stimulation. *J Neurophysiol.* **117**, 1000 – 1013.

Garden Terror - Case Series Of Twenty Eight Serious Ear Injuries Caused By Yucca Plants

A case series of yucca plant –induced ear injuries

Maria Vartanyan¹, Kumiko Orimoto ^{1,2}, Adrian Dragovic ^{1,2}, Carmel Crock ¹, Michael Dobson¹, Stephen O’Leary^{1,2}

¹The Royal Victorian Eye and Ear Hospital (RVEEH), Melbourne, Australia

² Dept. of Surgery –Otolaryngology, University of Melbourne

Introduction: The Yucca plant is common in Australia. Its sharp leaf spine is responsible for a substantial number of ear injuries in Melbourne. An electronic search yielded 28 patients presenting to the RVEEH with ear traumas caused by yucca between 2012 and August 2017.

Case series report: 25 patients had a tympanic membrane perforation, while trauma was confined to the ear canal in 3 cases. Perilymphatic fistula (PLF) complicated the course of penetrating ear injury in 4 cases. None of these patients had a positive fistula test, but all were dizzy with a sensorineural hearing loss. Two of our PLF patients had positive Dix-Hallpike test “masking” PLF, which delayed the diagnosis. One of patients presented with an acute otitis media complicated by labyrinthitis and early meningitis few weeks after initial trauma and PLF formation.

Discussion: Diagnosing inner-ear penetration by yucca plant is not straightforward because classical tests of PLF may be negative.

Conclusion: Combination of traumatic perforation by yucca plant, SNHL and/or vestibular symptoms should prompt urgent otological referral, as traumatic PLF is a surgical emergency because of the risk of a dead ear.

Key words: perilymphatic fistula; yucca plant; penetrating ear injury; fistula test; Dix-Hallpike.

iv. Acknowledgments

Stephen O’Leary is supported by a Practitioner Fellowship from the National Health and Medical Research Council.

The Vestibular System and Sleep

Shaun Watson, Neurologist
Prince of Wales Hospital, Sydney

We commonly refer to “falling” asleep. Is this metaphor or sensory reality? Consider the hypnic jerk during a boring lecture. Is an otolithic sensation of falling the primary phenomenon? Sleep is a complex series of states of the central nervous system that are actively initiated and maintained. During REM sleep, in particular, aminergic projections to the brainstem actively block sensory and motor traffic, so that the brain’s virtual reality magic lantern can play without sensory “enslavement” or motor consequences. A contemplation of dream structure and content suggests that vestibular afference is blocked during REM sleep but that vestibular experience can be rich. The dream self is embodied and the experience of flying, floating or falling is common and clearly independent of the sleeping posture.

Several vestibular disorders are postural/positional and typically occur in bed, most notably Benign Positional Vertigo and Postural Alcohol Nystagmus/Vertigo. Do these peripheral disorders manifest as vertigo during dreaming or is the vestibular afference blocked? Do central vestibular disorders such as vestibular migraine or height vertigo manifest during dreaming? While these speculations seem fanciful and distant from serious science and medicine, a better understanding of the mechanisms that modulate vestibular afference in dreaming could guide pharmacotherapy for peripheral and central disorders. A related and potentially clinically important area is the role of rhythmic vestibular afference in the induction of sleep, such as rocking and carrying of infants. Homework – a vestibular dream diary.

Reduced neurofilament protein expression and accumulation of lipofuscin in the lateral vestibular nucleus in Parkinson’s disease; a new insight into postural instability?

TP Wellings ^{*1,2,3}, AM Brichta ^{1,2}, R Lim ^{1,2}

¹ Faculty of Health and Medicine, The University of Newcastle, NSW, Australia, ² Hunter Medical Research Institute, Australia, ³ Department of Neurology, John Hunter Hospital, NSW, Australia

A common cause of morbidity and disability in Parkinson’s disease (PD) is postural instability. However, the neuropathology underlying postural instability is unknown. Postural reflex control is mediated by Deiters’ neurons of the lateral vestibular

nucleus (LVN), which are the brainstem origin of descending vestibulospinal reflexes. Deiters' neurons express the cytostructural protein, non-phosphorylated neurofilament protein (NPNFP). In PD, reduced expression of NPNFP in substantia nigra (SN) neurons is believed to contribute to dysfunction. Our aim was to determine if there is altered expression of NPNFP in the LVN in PD. We immunolabeled NPNFP in brainstem sections of six aged controls (mean age 92 yo) and six PD donors (mean age 83 yo) as well as two patients with progressive supranuclear palsy (PSP; mean age 77). Our results show there was a ~ 50% reduction in NPNFP-positive Deiters' neurons compared to controls ($13 \pm 2.0/\text{section}$ vs $25.7 \pm 3.0/\text{section}$; $p < 0.01$, repeated measures ANOVA). In contrast, there was no difference in NPNFP-positive counts in the facial nucleus between control and PD. The normalized intensity of NPNFP labeling in LVN was also reduced in PD (0.87 ± 0.05 vs 1.09 ± 0.03 ; $p < 0.01$). There was a 35% concurrent reduction in NPNFP-positive neuropil in PD relative to controls ($p < 0.01$). We also show there was an 84% increase ($p < 0.05$) in somatic lipofuscin in PD patients compared to control. Lipofuscin aggregation has been shown to increase not only with age but also with neurodegeneration. Furthermore, decreased NPNFP intensity was strongly correlated with increasing lipofuscin autofluorescence across all cases ($R^2 = 0.81$, $p < 0.01$). In contrast, there were no significant differences between PSP patients and controls. These results show two alterations in cellular content of Deiters' neurons of the LVN with PD, reduced expression and intensity of NPNFP and increased lipofuscin aggregation in Deiter's neurons. These changes may contribute to degeneration of postural reflexes observed in PD.

Who said there is no treatment for Tinnitus?

Dr Brian Williams and Ms K Lo.
71 Archer Street, Chatswood, Sydney

The aim of this study is to analyse the clinical results of patients treated for tinnitus in a multidisciplinary ENT and audiology clinic in Sydney using the Williams Tinnitus Treatment (WiTT[®]). All patients had initial full medical evaluation by an ENT including audiological assessment by an audiologist. 18 patients with moderate, severe or catastrophic tinnitus on Tinnitus Handicap Inventory (THI) were treated at the time of writing up this study using the WiTT[®]. Results and progress of patients were documented through the use of THI and verbally assessed numerical rating scale (NRS) assessments of tinnitus. THI and NRS results show statistically significant improvement in tinnitus after completing the WiTT[®]. 14 of the 18 patients who undertook WiTT[®] had prior tinnitus management elsewhere. Those 14 showed statistically significant improvement in THI and NRS after completing WiTT[®].

The Effects of Habitual Spectacle Use and Visual Acuity on the Video Head Impulse Test

Kyla KM Yamsuan, Peter R Thorne¹, Philip RK Turnbull², Rachael Taylor^{3,4}

¹Section of Audiology, University of Auckland

²School of Optometry and Vision Science, University of Auckland

³Whangarei Hospital

⁴New Zealand Dizziness and Balance Centre.

Background: The video head impulse test (vHIT) is a test of balance function, which records reflexive eye movement following brisk head rotations i.e., the vestibulo-ocular reflex (VOR). Studies suggest that the VOR for lower angular head velocities is affected by adaptation to spectacle lenses. However, there is a current gap in the literature regarding their effect on the vHIT, which utilizes natural high velocity head movements.

Objectives: This study sought the effects of habitual spectacle use and visual acuity on vHIT (GN Otometrics) outcome measures of gain and catch-up saccade presentation.

Methods: vHIT gains and rates of catch-up saccades were recorded from 25 individuals with no refractive error (13 females; mean age 24.4, range 17- 35 years) and 32 individuals with moderate to severe myopia; 21 (12 females; mean age 26.9, range 17-40 years) wore spectacles and 11 (9 females; mean age 29.0; range 21-39 years) wore contact lenses. Measurements for horizontal head impulses delivered in light and dark were compared between spectacle wearers and controls (no refractive error) using a repeated measures General Linear Mixed Model (GLMM). The effect of visual acuity was investigated in a separate analysis of results for the contact lens group by comparing gains obtained for their corrected (lenses in) and uncorrected (lenses out) vision.

Results:

Spectacle wearers demonstrated significantly lower vHIT gains ($p=0.003$) and higher rates of catch-up saccades ($p=0.054$) than controls with no refractive error. The mean gain difference of 0.035 (95% CI: 0.013 – 0.057) occurred irrespective of lighting, and higher power lenses were associated with a greater drop in gain, with an average 0.014 decrease for every diopter under -3.0D. Significant interaction effects were evident for the analysis of catch-up saccades; spectacle wearers demonstrated higher rates of catch-up saccades in light, but not in dark, and only when tested during the first half of the experiment. vHIT gains for contact lens wearers were not significantly different for corrected (lenses in) versus uncorrected (lenses out) vision ($p=0.115$), and uncorrected vision (left gain= 0.97 ± 0.03 ; right gain= 1.03 ± 0.04) yielded similar results to controls with no refractive error (left gain= 0.97 ± 0.04 ; right gain= 1.04 ± 0.04). There was no relationship between the severity of visual impairment and vHIT gains ($p=0.223$).

Conclusions: Habitual spectacle lens use for moderate-severe myopia causes vestibulo-ocular reflex adaptation, resulting in lower vHIT gains and higher rates of catch-up saccades. Although the effect size is small, clinicians should be aware of this association when interpreting vHIT results.