

# New methods for diagnosis and treatment of vestibular diseases

Stefan CA Hegemann<sup>1\*</sup> and Antonella Palla<sup>2</sup>

Addresses: <sup>1</sup>Department of ENT- HNS, Zurich University Hospital, 8091 Zurich, Switzerland; <sup>2</sup>Department of Neurology, Zurich University Hospital, 8091 Zurich, Switzerland

\* Corresponding author: Stefan Hegemann (stefan.hegemann@usz.ch)

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## Abstract

Dizziness and vertigo are common complaints, with a lifetime prevalence of over 30%. This review provides a brief summary of the recent diagnostic and therapeutic advances in the field of neuro-otology. A special focus is placed on the clinical usefulness of vestibular tests. While these have markedly improved over the years, treatment options for vestibular disorders still remain limited. Available therapies for selected vestibular diseases are discussed.

## Introduction and context

Dizziness and vertigo are common complaints. Recently, Neuhauser *et al.* published two papers that reported a one year prevalence of 20% and a one year incidence of 3% for dizziness and vertigo in a general population, with reported cases higher in women than men [1,2]. Moreover, the impact of dizziness on social and working life is considerable [3]. Half of the patients affected by dizziness feel that their efficiency at work has substantially dropped and one-quarter of patients even give up or change their work as a result of dizziness [3]. Here we aim to provide an overview on recent advances in the diagnosis and therapy of vestibular disorders.

## Assessment of semicircular canal function

Since the invention of the caloric test by Bárány about 100 years ago [4], caloric irrigation and rotatory chair tests were the primary methods used to investigate semicircular canal (SCC) function up until the end of the last century. These tests, however, have poor reliability, mainly due to the following disadvantages: caloric irrigation (i.e., the thermal gradient across the inner ear) depends on anatomical factors of the middle ear, temporal bone thickness, and on the technician's skills, and conventional rotatory chairs deliver rather low-testing stimuli (usually <100 deg/s peak velocity and between 0.1 and 2 Hz frequency) [5,6]. Both methods, moreover, are almost exclusively used for investigating

the horizontal SCC. In 1988, Halmagyi and Curthoys [7] introduced a new diagnostic method known as the head impulse test (HIT), which has the significant advantage of assessing the function of an individual SCC. It can be performed at the bedside and has been shown to have a high sensitivity (~70%) and specificity (~70%) for detecting horizontal peripheral vestibular hypofunction even when conducted by physicians that do not specialize in neuro-otology [8]. In contrast to the caloric irrigation and rotatory chair tests, the quantitative measurement of HIT performed by the dual search-coil method is technically complex and expensive and thus only available in tertiary referral centers, despite allowing functional testing of all six individual canals [9].

Direct comparison of the diagnostic utility of caloric irrigation, rotatory chair testing, and HIT is problematic, as these three methods probe different frequency ranges of vestibular function. In Ménière's disease, for example, it has been shown that low-frequency vestibular function as assessed by caloric irrigation is affected earlier than high-frequency vestibular function as investigated by HIT [10]. The opposite is observed in Fabry disease, a congenital lysosomal storage disease [11]. These differences possibly result from the affection of different types of hair cells on the cupula. Moreover, in vestibular neuritis (a sudden unilateral deficit of the peripheral vestibular organ), recovery of vestibular imbalance is

frequency dependent: while the low-frequency vestibular function determined by caloric irrigation becomes symmetrical, the high-frequency function assessed by HIT often remains impaired [12,13].

#### **Assessment of otolithic function**

Estimation of the subjective visual vertical (SVV) is a simple method to assess utricular otolith function. In general, it is performed with the subject sitting upright in a stationary position in darkness and adjusting a luminous line to match the perceived earth-vertical. SVV estimation might be normal in a patient with chronic unilateral peripheral utricular hypofunction tested in a stationary position, however, deficits may be unmasked during eccentric rotation or by off-vertical axis rotation (OVAR) because any utricular otolith function asymmetry will be enhanced, thereby increasing the likelihood of detection. Rotational testing, however, is technically demanding and OVAR can induce motion sickness. This explains why both tests have been applied relatively seldomly to patients.

#### **Recent advances**

##### **Diagnosis**

In recent years there have been major advances in the methods used to diagnose vestibular organ function, allowing much better and easier diagnosis in dizzy patients. Some of these advances have been outlined below.

##### *Assessment of semicircular canal function*

To allow a quantitative measurement of HIT in clinical practice, new testing methods like the Video-HIT [14-16] and the dynamic visual acuity (DVA) test [17-20] are in the process of development. The DVA test is an easy, accessible, and low-cost method. With the recent improvement of DVA test parameters [21], sensitivity and specificity for unilateral and bilateral vestibular loss have significantly increased to 100% and 94%, respectively, in comparison with the search-coil method to quantitatively assess HIT. A major disadvantage of the DVA test, however, is that it depends on the cooperation of the patient; if the patient is unwilling or unable to cooperate, the test cannot be evaluated. In contrast, Video-HIT is much less dependent on patient cooperation and has been shown to be equivalent to the search-coil method in detecting peripheral vestibular deficits [15].

##### *Assessment of otolithic function*

Click vestibular-evoked myogenic potentials (VEMPs) are saccular otolith-mediated short-latency reflexes recorded by electromyography from the ipsilateral sternocleidomastoid muscle in response to intense

auditory clicks [22]. VEMPs are technically easy to perform and have been helpful in the diagnosis of a relatively new vestibular entity, the superior canal dehiscence syndrome (SCDS) [23]. One should be aware of this entity in patients with chronic disequilibrium of unknown origin. The etiology is still unclear but there is evidence that it could be due to a developmental abnormality [24,25]. Recently, a simple method using ocular VEMPs (oVEMPs) to measure the utricular function was introduced [26]. The method measures potentials in the inferior oblique muscle, which are mainly caused by stimulation of the contralateral utricle. This method is at least as good at detecting utricular deficits as the SVV during eccentric rotation [27]. It also shows significant differences between controls and SCDS patients. [28]. Due to the aforementioned benefits, this method may lead to a better knowledge of the long-lasting effects of utricular lesions in patients. A recent study found chronic symptoms associated with isolated unilateral utricular deficit [29] although measured with the older method of eccentric rotation. According to this study, the current view that a unilateral otolithic lesion can cause only short-lasting symptoms may have to be changed. OVAR is another possibility to measure utricular function [30] but it is technically complex and almost always nauseogenic [31]. Overall, oVEMPs are definitely cheaper, technically easier, and less demanding for patients and investigators.

##### **Treatment**

##### *Treatments of peripheral vestibular disorders*

In patients with acute vestibular neuritis, treatment with methylprednisolone has been shown to significantly improve vestibular recovery [32]. Interestingly, treatment with methylprednisolone plus valacyclovir was not superior to treatment with methylprednisolone alone. It is surprising that the antiviral drug valacyclovir did not improve the outcome of vestibular neuritis, since the underlying etiology is thought to be viral. One possible reason might be that medication was initiated within 3 days after symptom onset during which viral replication could have already occurred.

Recently, a non-blinded, non-placebo controlled study of patients with Ménière's disease demonstrated the superiority of high-dose betahistine (48 mg three times daily) over low-dose betahistine (16-24 mg three times daily) [33]. Intratympanic steroid injection is another promising treatment for Ménière's disease, as suggested by several studies [34,35]; most of these, however, were not placebo-controlled either [34,35]. To date, it is still unclear what type of steroids for intratympanic injection are most effective, how often injections must be

repeated, and which time interval between injections is optimal.

While gentamicin is effective for reducing vertigo attacks in Ménière's disease [35], very recently it has also been shown to increase postural control after vestibular schwannoma resection in patients with preserved partial vestibular function treated with gentamicin and vestibular physical therapy before surgery (compared to physical therapy alone) [36,37]. Although only a relatively small number of patients were enrolled in these studies, these results suggest that patients with pre-operative gentamicin treatment might benefit in terms of faster vestibular recovery and/or central compensation.

#### *Treatments of central vestibular diseases*

Treatment of vestibular migraine often parallels that of migraine headache but, to date, no large randomized placebo-controlled studies looking into effective treatments for this condition exist [38]. This shortcoming is probably due to the lack of commonly-used diagnostic criteria for vestibular migraine.

Several retrospective and case studies have suggested that prophylaxis beta-blockers (metoprolol, propranolol) [39,40], tricyclic antidepressants (amitriptyline, nortriptyline) [41], the calcium antagonist flunarazine [39], the serotonin antagonist pizotifen [41,42], and the carbonic dehydrase inhibitor acetazolamid [43] may be effective in the treatment of vestibular migraine. For treatment of acute vestibular migraine, triptans [44,45] and vestibular suppressants [44] have been reported to be beneficial.

Recent advances have been made in the pharmacotherapy of central vestibular nystagmus. Aminopyridine is a promising treatment option, especially for downbeat nystagmus (DBN). In animal experiments, 4-aminopyridine (4-AP) has been shown to increase the excitability of cerebellar Purkinje cells [46]. A similar mechanism of 4-AP action is postulated in humans [47]. In patients with cerebellar diseases, 4-AP and 3,4-diaminopyridine (3,4-DAP), a related agent with similar pharmacologic effects, have been shown to effectively suppress DBN [48-49]. Moreover, 4-AP improves smooth pursuit eye movements and the gain of the vestibulo-ocular reflex function, and restores gaze-holding abilities [48,49], while 3,4-DAP reduces the gravity-dependent component of DBN [51,52] and improves postural stability [53]. Furthermore, in patients with episodic ataxia type 2, 4-AP can reduce the frequency of ataxic episodes [54].

## **Implications for clinical practice**

### ***Vestibular function assessment***

The implementation of the Video-HIT and DVA makes quantitative assessment of peripheral vestibular semi-circular canal function now possible in any clinical setting. Not only do Video-HIT and DVA help clinicians to diagnose a peripheral vestibular deficit, but they also assist in monitoring vestibular recovery, such as after vestibular neuritis.

VEMP should be performed whenever SCDS, a perilymphatic fistula, or a large vestibular aqueduct syndrome is suspected [55,56]. Typical VEMP responses in patients with these conditions show increased amplitudes and lowered thresholds compared with normal control subjects [57]. VEMPs can also be used to differentiate superior vestibular neuritis (i.e., the affection of the superior division of the vestibular nerve) from a total or inferior vestibular neuritis (i.e., the affection of the inferior division of the vestibular nerve), since in the former the saccular function is mostly spared and, thus, VEMP responses are normal. It has not yet been shown whether the little part of the sacculus being innervated by the superior vestibular nerve has a significant effect on the VEMP in superior vestibular neuritis.

### ***Treatments of peripheral vestibular disorders***

Clinicians are advised to initiate drug therapy in patients with vestibular neuritis with methylprednisolone (e.g., 100 mg/day for 7 days) within 1 week (or maybe even up to 4 weeks) after the onset of symptoms. The time of treatment onset for corticoid administration has not yet been studied and whether an increased dose (e.g., 250 mg/day instead of 100 mg/day methylpredisone) has a better effect is a matter of debate. In patients severely affected by vestibular neuritis, clinicians might consider the administration of valacyclovir (1000 mg three times a day for 7 days) if diagnosis is made within 3 days of symptom onset.

Since intratympanic steroid injections reach a higher level in the inner ear fluids than oral or intravenous administrations, this application technique may have a better effect in acute vestibulopathies. However, vestibular disorders are often thought of as being the result of nerve damage (neuritis), and it would be unlikely that the nerves would be reached by intracochlear steroids. No studies about intratympanic treatment exist, so this point has not yet been validated.

When treating Ménière's disease, intratympanic steroid injections are appropriate if the disease does not respond to conventional medical treatment with betahistine and

cinnarizine, and should be considered before more invasive and vestibulotoxic interventions like intratympanic gentamicin injections or surgery.

### Treatments of central vestibular diseases

When treating vestibular migraine, clinicians are advised to closely follow the treatments proposed by Neuhauser and Lempert [58] and are recommended to read a recent review by Lempert *et al.* on vertigo as a symptom of migraine [59]. Those making decisions about drug selection for the treatment of vestibular migraine should also consider potential side-effects, such as increased depression with flunarazine treatment or orthostatic hypotension with beta-blockers. A 50% reduction of attacks is a reasonable goal to aspire to [60]. It is advised that patients monitor the severity and frequency of attacks on a calendar and that the efficacy of drugs be evaluated after 3 months. Moreover, lifestyle modifications approved for migraine prophylaxis (e.g., regular exercise, sleep, and diet) should be discussed.

Finally, it has to be emphasized that from what is known so far, aminopyridine seems to be effective predominantly in patients with cerebellar atrophy and with DBN of an unknown etiology, and less effective in patients with structural cerebellar lesions [48,50,61].

### Abbreviations

3,4-DAP, 3,4-diaminopyridine; 4-AP, 4-aminopyridine; DBN, downbeat nystagmus; DVA, dynamic visual acuity; HIT, head impulse test; OVAR, off-vertical axis rotation; oVEMP, ocular vestibular evoked myogenic potential; SCC, semicircular canal; SCDS, superior canal dehiscence syndrome; SVV, subjective visual vertical; VEMP, vestibular evoked myogenic potential.

### Competing interests

The authors declare that they have no competing interests.

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