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Vestibular dysfunction: Prevalence, impact and need for targeted treatment

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This manuscript is the first in a series on vestibular neuropharmacology, and serves to establish why it is important to develop pharmacologic interventions to treat disorders of the vestibular system. We will review the prevalence of vestibular disorders, present studies that describe the impact of vestibular disorders on quality of life and clinically significant outcomes such as falls, and discuss the need for rational, targeted treatment. We will advance a central hypothesis, that for vestibular disorders with a well-defined pathophysiology, targeted, effective treatments exist.

The prevalence of vestibular disorders has been estimated in several population-based studies, and can be categorized into studies that evaluated a cardinal symptom of vestibular dysfunction, vertigo; studies that estimated vestibular function using balance testing, and studies that considered the prevalence of specific vestibular disorders. We will review each category of population-based study in this order. A study in Germany queried a representative sample of the population about vestibular vertigo, which was defined as rotational vertigo (illusion of self-motion or object motion), positional vertigo (vertigo or dizziness precipitated by changes of head position, such as lying down or turning in bed) or recurrent dizziness with nausea and oscillopsia or imbalance. Neurotologic interviews in 1003 subjects were used to validate the questionnaire. The study found lifetime adult prevalence of vestibular vertigo of 7.4%, a 4.9% 1-year prevalence, and a 1.4% 1-year incidence. Vestibular vertigo was 3 times more common in the elderly, and exhibited a nearly 3-fold female preponderance [27,29].

We recently estimated the prevalence of vestibular dysfunction in the US population using data from the 2001–2004 National Health and Nutrition Examination Survey (NHANES), where balance function was assessed using the modified Romberg test, an objective measure. We found that 35% of US adults age 40 years and older had evidence of balance dysfunction based on this postural metric [1]. The odds of balance dysfunction increased significantly with age, such that 85% of individuals age 80 and above had evidence of balance dysfunction. Additionally, the odds of balance dysfunction were found to be 70% higher among individuals with diabetes mellitus [1]. Dose-response relationships were observed, such that subjects with longer duration of disease and greater disease severity (as

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measured by Hemoglobin A1C levels) had poorer balance function. Moreover, patients with other diabetes-related complications, including peripheral neuropathy and retinopathy, were significantly more likely to have concomitant balance dysfunction.

Turning to specific vestibular disorders, benign paroxysmal positional vertigo (BPPV) is the most common vestibular disorder, and may account for up to one-third of vertigo presentations to dizziness clinics [26]. Based on a telephone survey of a representative sample of the adult German population, where BPPV was defined as at least 5 attacks of vertigo in last year lasting < 1 minute without concomitant neurological symptoms and invariably provoked by typical changes in head position, a 2.4% lifetime prevalence of BPPV was observed, along with 1-year prevalence of 1.6%, and a 0.6% incidence of new cases. BPPV was more common in older adults, with a prevalence of 3.4% in individuals over age 60, and the cumulative lifetime incidence was almost 10% by age 80 [36].

Vestibular migraine appears to be the second most common cause of dizziness. A survey of the German health system demonstrated a prevalence of vestibular migraine of 6–7% among patients who presented to a neurotology clinic, and a prevalence of 9% in patients who presented to a migraine clinic [26]. Using a telephone survey administered to a representative sample of the German adult population where vestibular migraine was defined as 1) recurrent vestibular vertigo; 2) migraine according to the International Headache Society; 3) migrainous symptoms during at least two vertiginous attacks (migrainous headache, photophobia, phonophobia, or aura symptoms); and 4) vertigo not attributed to another disorder, a lifetime prevalence of vestibular migraine of 0.98% was observed, as well as a 0.89% 1-year prevalence [28]. Additionally, vestibular migraine is the most common diagnosis in children with vertigo [12].

Several population-based studies have attempted to estimate the prevalence of Menière's disease. One study in the United States evaluated the number of new cases that presented to otolaryngologists at the Mayo Clinic (with a defined catchment population), where a case was defined as the presence of fluctuating/progressive sensorineural hearing loss with "spells" of vertigo. An annual incidence of 15.3 per 100,000 population was observed [40]. Another study conducted in Southern Finland used a questionnaire that asked whether individuals had experienced vertigo associated with a moving sensation, hearing loss, or tinnitus. After excluding subjects who may have had another reason for these symptoms such as former head trauma, ear surgery, stroke, noise exposure, epilepsy, specific provocative factors for vertigo (e.g. head movement), 16 positive responses out of 3138 surveys were collected for definite Menière's disease, equivalent to a prevalence of 515/100,000 [17]. Another more recent study looking at the US Health Claims Database identified 473,000 coded diagnoses of Menière's disease (ICD-9 386.0) in January 2005–2007 out of 60 million claims, equivalent to a prevalence of 190/100,000 [16].

The incidence of vestibular neuritis was estimated in a study in Japan, where it was found that 7% of patients presenting to dizziness outpatient clinics had evidence of vestibular neuritis, equivalent to an incidence rate of 3.5/100,000. Interestingly, a male predominance of vestibular neuritis was observed unlike other vestibular conditions where a female preponderance is typically observed [32]. The prevalence of superior canal dehiscence

syndrome (SCDS) is difficult to estimate, given that individuals who have a dehiscence may not always be symptomatic or may not have the diagnosis of SCDS. A study of cadaveric temporal bones does provide an approximation: A physical dehiscence of the superior canal was present in ~0.5% of 1000 cadaveric temporal bones, equivalent to a lifetime prevalence of 0.5% [7]. It should be noted, however, that this may be an overestimate given that these subjects did not necessarily exhibit the clinical manifestations of SCDS, and that donors to temporal bone registries may be more likely to suffer from otologic diseases.

The impact of vestibular disorders appears to be considerable. Individuals with vestibular vertigo in a study in Germany reported interruption of their daily activities, and the need for sick leave or medical consultation in 80% of subjects [27]. Another study evaluated the social impact of dizziness through the Social Life and Work Impact of Dizziness questionnaire administered in populations in Italy and England. Twenty-seven percent of subjects with dizziness reported changing jobs, 21% gave up work, and 50% reported reduced efficiency at work. Fifty-seven percent reported a disruption in their social life, 35% reported family difficulties, and 50% reported difficulties with travel [5].

Vestibular disorders have also been shown to impact mood and cognitive status. Patients who presented to a neurotology clinic with a documented vestibular disorder experienced greater than expected anxiety and depression distress [25]. Individuals with vestibular disorders also frequently report cognitive impairment or "brain fog" as well as difficulties in spatial memory/attention. Decreased hippocampal size has been observed in patients with bilateral vestibular loss [15,33].

Some of the more striking evidence of the impact of vestibular disorders comes from the study of the quality of life (QOL) in individuals with specific vestibular disorders. A study in which the QOL index Short-Form 36 was administered to patients with Meniere's disease demonstrated that Menière's disease has a similar impact on QOL as chronic health problems, and that vertigo symptoms have the greatest impact on QOL [41]. Another study evaluated the comparative QOL associated with Meniere's disease, and found that active Menière's disease had a QOL that was intermediate between Alzheimer's disease not requiring institutionalization, and patients with AIDS or cancer, 6 days before death [3].

The impact of vestibular disorders may also be determined based on the increased risk of clinically significant outcomes such as falls. In the previously-mentioned study using data from NHANES, individuals with balance dysfunction had a 2.6-fold increase in the odds of falling, and those who were clinically symptomatic (i.e. reported dizziness) had a 12-fold increase in the odds of falling. Falls are a highly prevalent event among older individuals: over 1 in 3 community-dwelling adults age > 65 fall each year. Falls exert a tremendous individual and societal toll: 10% of falls result in major injuries such as hip fractures, falls with injury increase the risk of nursing home placement 10-fold, and the costs of falls in the United States are estimated to exceed \$20 billion annually [11,13,34,35].

The central hypothesis of this paper is that for vestibular disorders with well-defined pathophysiology, targeted, effective treatments exist. We will provide several examples to support this hypothesis, and allow this hypothesis to set the stage for the subsequent papers

on vestibular neuropharmacology. BPPV is an example of a vestibular disorder whose pathophysiology is well-understood and for which an effective treatment exists based on this pathophysiologic understanding. BPPV results from the displacement of otoconia from the utricular macular to the semicircular canals, typically to the posterior canal. Treatment of BPPV involves repositioning maneuvers, which move otoconia out of the affected canal and into the vestibule, where they are thought to dissolve. For example, the Epley maneuver uses gravity to treat canalolithiasis of the posterior canal by moving the patient through 4 positions with each position maintained for 30 seconds to allow settling of the particles to the lowest gravitational position. Strong evidence from numerous studies suggests that particle repositioning therapy reduces symptoms of BPPV and results in a conversion from a positive to negative Dix-Hallpike maneuver in up to 80% of patients [19–21].

Superior canal dehiscence syndrome (SCDS) is another example of a vestibular disorder where the pathophysiology is well-established and a targeted, effective treatment has been developed. In SCDS, a third mobile window into the middle cranial fossa produces the symptoms of sound-induced vertigo (Tullio's phenomenon), pressure-induced vertigo, boneconduction hyperacusis, and autophony. The diagnosis is made based on a high-resolution CT scan of the temporal bone, which demonstrates a dehiscent superior semicircular canal. Plugging the dehiscent canal via middle fossa craniotomy, which eliminates the third mobile window, has been shown to decrease symptoms, normalize physiologic testing including vestibular-evoked myogenic potentials (VEMPs) and the audiometric air-bone gap, and improve quality of life based on the Dizziness Handicap Inventory (DHI) [8,9,24].

As a corollary to our central hypothesis, for vestibular disorders with poorly-defined pathophysiology, there is limited evidence for targeted, effective treatments. An example of a poorly-understood vestibular disorder is vestibular deficiency associated with aging, or presbystasis. As discussed previously, we observed using population-based data from NHANES that the prevalence of balance dysfunction increased significantly with age. Based on these findings we sought to further characterize the changes in vestibular physiologic function associated with aging. First, we evaluated whether age-related deficits occur symmetrically or selectively across the 5 vestibular end-organs - the 3 semicircular canals (horizontal, superior and posterior) and 2 otolith organs (saccule and utricle). We conducted a pilot study characterizing semicircular canal and otolith function in 50 healthy individuals age 70 and above. We used dynamic visual acuity during head thrusts (htDVA) as a measure of semicircular canal function, based on prior data from our laboratory demonstrating that the htDVA test is highly correlated with search coil testing while being significantly less time- and resource-intensive to administer [31]. We used air-conducted sound-evoked cervical vestibular-evoked myogenic potential (VEMP) testing as a measure of saccular function, and midline skull tap-evoked ocular VEMP testing to assess utricular function, based on studies demonstrating the validity of these otolith-specific measures [38,39]. We found that vestibular function declined asymmetrically across the vestibular end-organs: 80-90% of individuals age 70 and above had evidence of semicircular canal dysfunction, whereas only 50% of participants had abnormal saccular function and 20% had utricular impairment. Interestingly, histopathologic analyses of age-related changes in the temporal bone corroborate these findings, demonstrating a greater loss of vestibular hair cells in the cristae ampullares of the semicircular canals relative to the otolithic maculae [30].

At present, treatment options for presbystasis, and bilateral vestibular deficiency (BVD) in general, are limited. Vestibular rehabilitation is a mainstay of treatment, whereby patients compensate for their vestibular loss by using visual or proprioceptive cues under the direction of a therapist [6,23]. Other options include the use of sensory substitution methods such as biofeedback prostheses, whereby a body-worn device delivers sensory feedback (e.g. vibrotactile, auditory) to patients to orient the trunk during body sway [4,14,18,22,37]. However, strong, systematic evidence in support of rehabilitative strategies for the treatment of BVD and the improvement in clinically-significant outcomes (e.g. quality of life, falls) is lacking. The multi-channel vestibular prosthesis represents a promising new technology for the treatment of BVD that is awaiting human trials [10].

In this paper we have demonstrated that vestibular disorders are quite prevalent, and that the impact on overall health and well-being are considerable. The urgent need for treatment is a function of both the prevalence and impact of vestibular disorders. This need is exemplified in the case of presbystasis, which appears to be highly prevalent among older individuals and results in significant morbidity including falls. We have suggested that for vestibular disorders with well-defined pathophysiology, targeted, effective treatments exist. Although the particular treatments we reviewed were not pharmacologic, the treatment of Menière's disease, vestibular migraine, and the behavioral consequences of chronic vertigo (e.g. the anxiety, phobia and motion sickness associated with chronic subjective dizziness) represent important potential targets for pharmacologic intervention. The development of effective treatment modalities will require a heightened understanding of the pathophysiologic basis of vestibular disease, followed by controlled studies on the efficacy of pharmacologic interventions in the treatment of vestibular disease.

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