Recent Advances in the Diagnosis of Audio-vestibular Disorders

Running head: Advances in the Diagnosis of Audio-vestibular Disorders

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Abstract

In the present concise review of the recent literature, the new interdisciplinary paradigm of audiovestibular medicine as a challenge to theory and clinical practice is presented. Most common symptoms include dizziness, vertigo, tinnitus, nystagmus, and hearing loss. Several conventional and newly-introduced methods for the precise diagnosis of audiovestibular disorders and their applications are illustrated. The need for further interdisciplinary research by national and international teams of otologists, neurootologists and specialists of vestibulology is emphasized.

Keywords: audiovestibular medicine, auditory disorders, vestibular disorders, diagnosis

Audiovestibular medicine - a new paradigm

Recently, a new promising interdisciplinary field has emerged in the expanding otoneurology domain. It deals with effective and fruitful integration of a variety of basic and clinical disciplines resulting, at the same time, in a narrow differentiation and gradual institutionalization of this hot topic of rising socio-medical importance worldwide.

Symptoms referable to disorders affecting the inner ear and vestibulocochlear nerve include dizziness, vertigo, tinnitus, and hearing loss, in various combinations (1). Similar symptoms may occur with involvement of the central nervous system, principally the brainstem and cerebellum, to which the vestibular and auditory systems are connected. Bony structures are primarily assessed by computed tomography while soft-tissue ones - by magnetic resonance imaging (MRI). In suspected vascular lesions, angiography or venography should be obtained while no neuro- or audiovestibular imaging is needed in patients with typical presentations of common peripheral vestibular or auditory disorders.

The guidelines of the French Otorhinolaryngology-Head and Neck Surgery Society (SFORL) for diagnostic and therapeutic strategy in Menière's disease are presented (2). Menière's disease is diagnosed in the presence of the association of four classical clinical items and after eliminating differential

diagnoses on MRI. In case of partial presentation, objective audiovestibular tests are recommended. Following ear-nose-throat examination and audiovestibular tests, the Dokuz Eylül University Meniere's Disease Disability Scale (DEU-MDDS) and Turkish version of the Dizziness Handicap Inventory (DHI-T) are administered to 93 definite Meniere's disease patients at a mean age of 48.9 ± 12.1 years in Izmir, Turkey (3). Cronbach's alpha is 0.92 and intraclass correlation coefficients of the DEU-MDDS are statistically significant ($p < 0.001$). The correlation coefficients of each item with the scale are sufficient. The MDDS is a valid and reliable scale as a disease-specific quality of life questionnaire for Meniere's disease patients.

The diagnostic process in patients presenting with a variety of audiovestibular symptoms should begin with individual medical and family history followed by traditional audiovestibular tests. The most important audiological test battery in all cases should include pure tone audiometry possibly extended to the high-frequency region, transient evoked otoacoustic emissions, distortion product otoacoustic emissions, and auditory brainstem responses (4,5). Vestibular testing should include a basic vestibular examination integrated with caloric test, vHIT, and VEMPs (5). The aforementioned test batteries should be performed at the onset of the audiovestibular symptoms and during follow-up to monitor the course of the disease.

The analysis of the relationships between tumour size, hearing, and vestibular outcomes in 124 patients with unilateral extrameatal vestibular schwannoma undergoing preoperative audiovestibular investigations such as audiometry, discrimination test, caloric test, cervical vestibular evoked myogenic potential and ocular vestibular evoked myogenic potential reveals significant a difference between lesioned and non-lesioned ear for all audiovestibular outcomes (6). Cervical vestibular evoked myogenic potential deficit is significantly associated with severe hearing loss and larger tumours.

The agreement between the protocols of Oxford, Northern, Charing Cross, and Nashville guidelines for the investigation of asymmetrical audiovestibular symptoms by means of retrospective audit of the indications for arranging 854 consecutive magnetic resonance imaging scans of the internal auditory meatus is determined (7). The level of agreement is low, with kappa values ranging between 0,15

and 0,58 between these protocols. This study highlights another area of difficulty when determining which patients with audiovestibular disorders to investigate.

The results of 678 cerebellopontine angle lesions in 340 patients with asymmetrical audiovestibular complaints comparatively examined by high-resolution T2-weighted and gadolinium enhanced T1-weighted MRI are analyzed (8). The sensitivity and negative predictive value of the first method are 90% and 99.5%, respectively. Additional use of the second method further increases the sensitivity and negative predictive value of the first method up to 93% and 99.7%, respectively.

Ten patients, eight males and two females, aged between 38 and 76 years who have developed acute audiovestibulopathy in association with embolic labyrinthine infarction in the non-anterior inferior cerebellar artery territories are examined by audiometry, head-impulse tests (HTI), or caloric tests (9). There is a combined audiovestibulopathy in six patients, isolated vestibulopathy in three and isolated hearing loss in one patient. The MRI proves single or multiple infarctions in the cerebellum or cerebral hemispheres in five patients each.

The retrospective analysis of the National Collegiate Athletic Association Injury Surveillance System of the USA from 2009 through 2014 for seven men's sports and eight women's sports shows 1647 recorded sports-related concussions (10). The most common audiovestibular symptoms are dizziness (in 68.2%), imbalance (in 35.8%), disorientation (in 31.4%), noise sensitivity (in 29.9%), and tinnitus (in 8.5% of the cases). Overall symptom duration and return to competition time are statistically significantly higher in the presence of these symptoms ($p < 0.05$). Duration of concussion symptom correlates with dizziness ($p = 0.043$) and noise sensitivity ($p = 0.0001$), whereas return to participation times correlates with imbalance ($p = 0.011$) and noise sensitivity ($p = 0.0001$). Dizziness and imbalance (odds ratio of 4.15; between 3.20 and 5.38; $p < 0.001$) are the two symptoms with the strongest association.

The patterns and mechanisms of audiovestibular impairments associated with intracranial hypotension are investigated in 16 patients by using tridimensional video-oculography for spontaneous, gaze-evoked, and positional nystagmus (11). Pure tone audiometry and bithermal caloric tests are applied, too. In five patients, there are neuro-

otological symptoms along with the orthostatic headache while laboratory evaluation demonstrates audiovestibular impairments in ten patients. Oculographic analyses document spontaneous and/or positional nystagmus in six patients including weak spontaneous vertical nystagmus with positional modulation (in four) and pure positional nystagmus (in two patients). One patient presents with recurrent spontaneous vertigo and tinnitus mimicking Meniere's disease and shows unidirectional horizontal and torsional nystagmus with normal head impulse tests during the attacks. Audiometry indicates unilateral (in six) or bilateral (in one) sensorineural hearing loss.

The clinical usefulness of MRI of the temporal bone is evaluated in 1263 patients at a mean age of 46.97 ± 16.95 years with facial and audiovestibular dysfunction (12). Hearing loss is established in 429, vertigo - in 397, tinnitus - in 341, and peripheral facial palsy - in 96 patients. There are positive MRI findings possibly responsible for clinical manifestations in 232 patients (in 18.37% of the cases) as follows: in 86 patients (in 20.05%) with hearing loss, in 21 (in 21.88%) - with facial palsy, in 62 (in 18.18%) - with tinnitus, and in 63 (in 15.87% of the cases) - with vertigo.

In six patients with superficial siderosis diagnosed by MRI, it deals with a sensorineural hearing loss, cerebellar ataxia with combined central and peripheral vestibulopathy on both sides (in four), as well as a bilateral peripheral vestibulopathy or isolated central vestibulopathy (in one patient each) (13). There is progressive hearing loss over year in five patients which is asymmetric in four of them. The cochlea-vestibular dysfunction generally progresses asymmetrically without any left-right asymmetry on MRI.

There are incidental findings in 50.5% of 109 MRI scans of the internal auditory meatus for audiovestibular symptoms performed in a radiology department at a UK district general hospital (14).

Vestibular diagnostics

Symptoms of vertigo and dizziness originate from otological, neurological, medical and psychiatric etiologies and represent an interdisciplinary challenge (15). The most important criteria for differentiation are the timeline, quality of symptoms, modulating factors and accompanying symptoms. The following tests are relevant: head impulse test, test for spontaneous nystagmus, positional nystag-

mus, central ocular motor signs and the Romberg test. Occlusion of the anterior inferior cerebellar artery results in labyrinthine and cerebellar ischemia and causes acute vestibular syndrome and unilateral hearing loss. The diagnostic algorithm in the workup of patients with vertigo and dizziness should always include tests for peripheral and central vestibular and ocular motor function.

Vestibular function tests, including caloric, rotary chair, and vestibular-evoked myogenic potential (VEMP) tests, are used to assess the integrity of the vestibulo-ocular reflex and the vestibulo-colic reflex (16). Posturography is applied to quantify the relative contributions of sensory systems to postural control in the upright stance under either static or dynamic conditions. It provides insight into the presence of postural instability and helps identify which sensory system is involved, although it does not provide a topographic diagnosis.

The Practice Guidelines for the Diagnosis and Management of Benign Paroxysmal Positional Vertigo of the Otoneurology Committee of Spanish Otorhinolaryngology and Head and Neck Surgery are based on the Barany Society criteria for the diagnosis of this most frequent episodic vestibular disorder (17). This guideline provides recommendations on each variant of benign paroxysmal positional vertigo, with a description of the different diagnostic tests and the therapeutic manoeuvres.

Since three decades, auditory stimulated VEMPs recorded by using surface electrodes are used clinically to assess vestibular function (18). There are two types: cervical vestibular-evoked myogenic potential (cVEMP) and ocular one (oVEMP). They are elicited by auditory stimuli such as clicks, short tone bursts or tapping. The cVEMPs are recorded from the sternocleidomastoid muscle in order to evaluate the function of the saccule and the inferior vestibular nerve. According to physiological and clinical studies, these potentials to air conducted sounds reflect the function of saccular afferents. The use of galvanic stimulation together with air conducted sounds or bone conducted stimulation enables the differentiation of labyrinthine lesions from retrolabyrinthine ones. The accurate determination of the location of lesions is useful for studying the pathophysiology of vestibular diseases (18).

The analysis of 180 patients with vestibular complaints examined with a full battery of vestibular assessments including VEMP testing and comput-

erized dynamic posturography establishes the same rate of VEMP abnormalities in patients with normal and those with abnormal computerized dynamic posturography (19). However, these modalities measure different things and are all important in the diagnostic armamentarium.

Persistent postural-perceptual dizziness is a relatively new diagnosis for a balance disorder. The systematic review of 15 out of a total of 318 articles retrieved from several data-bases such as *CINAHL*, *EMBASE*, *PubMed (MEDLINE)*, *PsycINFO* and *Google Scholar* demonstrates that this is a maladaptive state to a variety of insults, including vestibular dysfunction rather than a structural or psychiatric one (20). Persistent postural-perceptual dizziness is useful as a diagnosis for otologists treating dizziness as it helps to define a conglomeration of symptoms that can seem otherwise vague.

There are abnormal vestibular testing results in 35 out of 188 pediatric patients (in 18.62% of the cases) at a mean age of 13.9 ± 3.56 years (range 2-17 years) (21). The patients unable to complete all the vestibular testing aspects can still do an average of 7.9 ± 4.0 of 12 test components. Failure to perform Nylen-Barany positional testing ($p = 0.0001$) or Dix-Hallpike ($p = 0.0174$) testing is associated with inability to obtain final diagnosis on vestibular testing.

A structured clinical examination including the head impulse test, an alternating cover test to detect a skew eyes' deviation and observation of nystagmus in different positions of gaze and using Frenzel goggles enables a reliable differential diagnosis of central or peripheral disorders in acute vestibular syndrome (22).

Among 560 patients in a pediatric vestibular clinic, 86 children (15.36% of the cases) at a mean age of 13.9 ± 4.7 years present with spontaneous nystagmus recorded by videonystagmography and half of them have horizontal nystagmus with a fixed direction (23). In most children (66 or 76.74%), there is no fixation only and a peripheral vestibular disorder such as vestibular neuritis or vestibular migraine is diagnosed in 68% of the cases while in 16 patients (18.60%), the spontaneous nystagmus is with and without fixation. There is vertical nystagmus in 15 patients, mainly with central vestibular disorders. Furosemide-loading vestibular-evoked myogenic potential is a new examination for the diagnosis of endolymphatic hydrops and Meniere's disease (24). The results of the video HIT (vHIT) corre-

spond with those of caloric testing in cases with vestibular neuritis but not in those with Meniere's disease. The inferior vestibular neuritis, a new concept in vestibular disorders, should be diagnosed by using vHIT and VEMP.

The glycerol cVEMP test and the cVEMP tuning property test are recently introduced (25). The fist method is time-consuming and can cause nausea or headache while the second one does not provide information when subjects do not show responses to either 500 Hz or 1000 Hz tone bursts. The air-conducted-sound oVEMP test is very useful for the physiological diagnosis or screening of superior canal dehiscence syndrome.

In the audiovestibular medicine department of the Royal Surrey County Hospital, Guildford, UK, two cases with congenital congenital canal paresis are reported (26). In them, caloric testing indicates an absent or significantly reduced response on the horizontal semicircular canal plane while vHIT shows near-normal or normal vestibulo-ocular reflex gain on the same plane.

Benign paroxysmal positional vertigo is assessed by means of dizziness handicap inventory, for symptom severity, functional gait and accelerometer in five conditions for postural sway (27).

The occurrence and intensity of vertigo attacks, hearing loss, tinnitus, and aural fullness in 192 clinically definite Meniere's disease patients is analyzed (28). The relationship between the extent of endolymphatic hydrops visualized by locally enhanced inner ear MRI and the severity of audiovestibular symptoms is assessed. There is no significant correlation between the extent of cochlear or vestibular hydrops and the number of definite vertigo days, neither in a short-term, nor in a middle-term time period.

Four patients with superior canal dehiscence syndrome are prospectively examined with oVEMPs and cVEMPs within a standard audiovestibular test battery (29). The increased oVEMP amplitudes have a specificity of 100%. Caloric function and vHIT are normal. Tullio sign and marked fremitus nystagmus are observed in two patients each. Three patients have autophony. The air-bone gap is < 10 dB in all patients. The computed tomography imaging shows a bony dehiscence of the superior semicircular canal in all patients.

In 375 successive patients with audiovestibular diseases such as unilateral ($n = 174$) and bilateral ($n = 51$) Meniere's disease, sudden deafness with

vertigo ($n = 70$) and vestibular neuritis ($n = 80$), vertigo frequency, persistent nystagmus and ipsilateral/contralateral hearing levels are recorded (30). There are neurosis and depression in 62.7% and 82.4% of bilateral Menière's disease patients, 32.7% and 48.9% of unilateral Menière's disease ones, 15.7% and 38.6% of sudden deafness/vertigo, and 12.7% and 31.3% of vestibular neuritis patients. Menière's disease with longer disease duration ($p = 0.021$) and worse hearing in the secondary affected ear ($p = 0.042$), sudden deafness/vertigo with persistent nystagmus ($p = 0.005$) as well as vestibular neuritis with longer disease duration ($p = 0.019$) and persistent nystagmus ($p = 0.0003$) are statistically significantly more common with mental disorders than those with shorter-duration disease, better hearing and no persistent nystagmus.

The relationship between vestibular abnormalities detected by vHIT for evaluation of the six semi-circular canals' function and long-term exposure to occupational noise is analyzed in 36 male industrial workers (aged 28-55 years, at a mean of 44.4 ± 6.1 years) with noise-induced hearing loss and a control group of 30 healthy men (aged 34-50 years, at a mean 41.1 ± 4.5 years) without hearing loss (31). There is canal deficit in 20 patients (in 55.5%) in the noise exposure hearing loss group and in two participants (in 6.6% of the cases) in the control one. There is a statistically significant capacity loss for vestibulo-ocular reflex gain in patients with noise exposure hearing loss.

The vestibular function and its eventual changes after stapes surgery is evaluated within a prospective case-control study in 20 patients (aged 33-58 years, at a mean age of 44 years) affected by otosclerosis that is considered one of the most common causes of hearing loss in adults, with a prevalence of 0.3%-0.4% in Caucasians (32). Audiological tests as well as cVEMP test and vHIT are used. In the patients, the mean values of the vHIT gains are 1.3 on the right and 1.01 on the left side. A statistically significant lower left gain is registered in the control group. There is a statistically significant postoperative reduction of P1/N1 amplitude in the patients complaining of postoperative dizziness or vertigo.

Audiovestibular loss of a vascular cause

Acute audiovestibular loss is characterized by abrupt onset of prolonged (lasting days) vertigo and hearing loss (33). Acute ischemic stroke in the

distribution of the anterior inferior cerebellar artery is the leading cause of acute audiovestibular loss. Unlike inner ear dysfunction of a viral cause, which commonly presents as an isolated vestibular (i.e., vestibular neuritis) or cochlear loss (i.e., sudden deafness), labyrinthine dysfunction of a vascular cause rarely results in isolated loss of vestibular or auditory function. As audiovestibular loss may precede the central symptoms of an ischemic stroke in the posterior brain circulation, its early diagnosis and proper management may provide a window to prevent the progression of such as cerebral infarction.

Territorial strokes of the anterior inferior cerebellar artery are commonly associated with basilar artery branch occlusive disease and audiovestibular loss is usually caused by its thrombotic narrowing of this artery, or the basilar artery at its orifice (33). In 2-3% of the cases, the internal auditory artery is a branch of the posterior inferior cerebellar artery, which explains the acute audiovestibular loss associated with cerebellar infarction in the territory of the posterior inferior cerebellar artery.

Acute unilateral peripheral vestibulopathy can be differentiated from posterior circulation stroke in acute vestibular syndrome by the most sensitive horizontal HIT while skew deviation is the most specific but non-sensitive sign (34). Video-oculography-based HIT has an additional power in this respect. Further refinement in video technology, increased operator proficiency and saccade analysis incorporation increases video-oculography-based HIT sensitivity of posterior circulation stroke diagnosis.

A patient with isolated audiovestibular loss shows a small infarction restricted to the root entry zone of the eighth nerve in the brainstem, suggesting that this zone is a candidate site responsible for isolated audiovestibular loss (35).

A 67-year old man complains of sudden left hearing loss and vertigo and shows left horizontal gaze-evoked nystagmus along with positive HIT on the left side (36). Videonystagmography reveals spontaneous rebound nystagmus and head-shaking nystagmus toward the right side. Pure tone audiometry proves severe sensorineural hearing loss on the left side. Temporal bone MRI demonstrates multifocal acute infarctions in the left side as well as tiny infarctions along the left vestibulocochlear nerve and the cochlea implying acute infarction of this nerve and labyrinth.

Audiovestibular symptoms in systemic autoimmune diseases

Recently, the comprehensive literature dealing with the diagnosis of audiovestibular disorders in patients with a variety of systemic autoimmune and autoimmune-mediated diseases has been systematized (37,38). The clinical presentation and diagnosis of immune-mediated inner ear diseases including autoimmune inner ear disease, Meniere's disease, bilateral vestibulopathy, as well as of systemic autoimmune diseases with audiovestibular disorders such as Behçet's disease, Cogan's syndrome, sarcoidosis, autoimmune thyroid disease (Hashimoto's thyroiditis), Vogt-Koyanagi-Harada syndrome, relapsing polychondritis, systemic lupus erythematosus, antiphospholipid syndrome, IgG4-related disease, and anti-neutrophil cytoplasmic antibody-associated vasculitides are described (37). Other autoimmune diseases associated to audiovestibular symptoms include mixed cryoglobulinemia, giant cell arteritis and ulcerative colitis (38).

The audiovestibular symptoms in systemic autoimmune diseases are often related to the entity of the autoimmune damage, as they may follow an inflammatory process in the inner ear or a direct macrophage aggression of the inner and - mainly - outer hair cells (39).

The sensorineural hearing loss is the most common auditory symptom of systemic autoimmune diseases (4), but due to its different presentation forms (sudden or progressive) and severity (mild to severe), an early correlation between the symptom and the systemic autoimmune disease is difficult to reveal. Audiovestibular symptoms in autoimmune diseases are common to other pathology such as diabetes mellitus and arterial hypertension. Therefore, a correct differential diagnosis of the cause of the audiovestibular involvement is of utmost importance.

The audiovestibular symptoms present in systemic lupus erythematosus patients follow antibody/antigen direct reactions, cytotoxic action, or immune complex deposition (39). Vasculitis following immune complex deposition is the major cause of cochlear and vestibular damage in such patients. The sensorineural hearing loss is the most common audiovestibular symptom with a prevalence of between 6% and 70%. Tinnitus is often associated with hearing loss in systemic lupus erythematosus following peripheral deafferentation (40).

The prevalence of audiovestibular symptoms is 8% to 65% of Wegener's granulomatosis patients, mainly with conductive hearing loss in cases of Wegener's granulomatosis involving the middle ear (38). Audiometric patterns of Wegener's granulomatosis are typically flat, although sometimes additional high frequency losses may coexist and differential diagnosis with noise exposure or age-related hearing loss is difficult. Hearing impairment may also present as sudden sensorineural hearing loss.

The stapedial reflex decay test is in myasthenia gravis patients and can be used as an additional tool for diagnosis and monitoring (41). Transient evoked and distortion product otoacoustic emissions are the main diagnostic tool for monitoring outer hair cell functionality in such patients. They are used to record subclinical hearing alterations before the onset of clinically evident hearing loss.

In multiple sclerosis, the autoimmunity mechanisms also affect inner ear structures; hair cells and auditory and vestibular spiral ganglion neurons are subject to the attack of lymphocytes, and their damage presents with sensorineural hearing loss and vertigo. M1 phenotype microglia can demyelinate cochlear and vestibular structures causing sudden sensorineural hearing loss or vertigo. Hearing loss occurs when multiple sclerosis involves both the peripheral and the brainstem auditory pathways (42). Audiovestibular symptoms in young, neurologically normal subjects, especially when spontaneous recovery occurs, could represent an early sign of multiple sclerosis even when no demyelinated plaques are visible in the central nervous system. It is recommended to evaluate these subjects with clinical, radiological, and electrophysiological tests to exclude peripheral incipient multiple sclerosis.

Cogan's syndrome is a rare autoimmune disorder characterized by audiovestibular dysfunction and ocular inflammation (43). Currently, there is no specific serum autoantibody used in its diagnostic workup yet. Despite medical treatment, hearing loss may progress to irreversible bilateral profound sensorineural hearing loss in approximately half of the patients resulting in candidacy for cochlear implantation.

Further interdisciplinary research by national and international teams of otologists, neurootologists and specialists of vestibulology could contribute to solve the difficult diagnostic problems of this socially significant pathology.

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