Clinical Advances and issues in Auditory and Vestibular Medicine

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Introduction

Recent advances in basic science, technology and treatments have increased our abilities to manage hearing and balance diseases more effectively. Advances in molecular genetics have allowed better understanding of congenital and hereditary hearing loss. The advent of regenerative medicine led to auditory hair cell regeneration in laboratory animals. Advances in hearing aids, cochlear implants and implantable middle ear devices have helped more effective management of hearing loss particularly in pediatric population.

The molecular biology and ionic transport between the stria vascularis and endolymph provided additional support for "Old" and "New" treatments of Menière's disease. The videonystagmography (VNG) technology has made it easier to observe and/or record vestibular responses. These responses are the ocular response (VOR) and visual vestibular interaction (VVOR). The vestibular spinal response (VSR) can be evaluated using a high compliance foam pad in addition to routine examination of stance, gait and postural stability.

Advanced audiometric and vestibular testing, stress Electrocochleography (ECoG) and Vestibular evoked myogenic potentials (VEMP) have increased our diagnostic acumen. High-resolution CT scans, MRI with DWI of the temporal bone and the brain allowed the visualization of inner ear anomalies such and brain lesions that were undetectable with traditional imaging. The further understanding of migraine and its association with chronic motion intolerance, vertigo and hearing loss has improved our clinical ability to treat these patients. New clinical entities such as autoimmune inner ear disease, vestibular migraine, superior canal dehiscence, benign intracranial hypertension, auditory neuropathy have been identified and managed more effectively.

Relatively new treatments such as inner ear perfusion with Gentamicin and Dexamethasone have helped controlled Meniere's disease and treat sudden sensorineural hearing loss. The purpose of this overview is to address the advances and the clinical issue pertaining to Auditory and Vestibular disorders.

Molecular and ionic dynamics of the endolymph and stria vascularis

Recent studies of the inner ear molecular homeostasis have shown that the auditory and vestibular functions are dependent on active transport of ions (K+, Na+) and water between inner ear compartments, especially within the scala media[1-3]. The normal stria vascularis has several ion, water and steroids channels and receptors. Ionic channels move K+ into the endolymph and Na+ out of the endolymph which is critical to generate and maintain normal electrical potentials of cochlear and vestibular hair cells. Active water channels (aquaporins) play a major role in the maintenance of intracellular osmotic pressure[4,5]. Steroids exert positive effects on the inner ear stria vascularis and its function.

In several animal studies, auditory-evoked brainstem response (ABR) thresholds and histopathology of the stria were improved, or stabilized, in treated animals by comparison to untreated controls. Aldosterone in particular has been shown to have most positive effects on reversing stria pathology[6]. This finding explains, for the first time in our literature, why a low salt diet has been helpful to most, but not all, patients with Menière's disease. A low salt diet increases systemic aldosterone via the reninangiotensin cascade, which leads to increased aldosterone concentration; hence, its positive effects on the inner ear homeostasis.

With added new knowledge in this area, we should be able to redefine conditions like Menière's disease and sudden hearing loss in terms of their underlying molecular dysfunction. Ultimately, intratympanic perfusion of different medicines and genetic vectors via the round window will be the optimal method to treat most inner ear disorders.

Office Neurotologic Examination

Traditional ENT and neurological examinations are usually normal in patients with hearing loss (mostly non infectious types) and vestibular disorders. This is based on traditional teaching and practice probably worldwide.

However, some institutions have changed their practice over the years, particularly in Europe and more recently in the USA, to include office neurotological examinations of these patients. Recent knowledge of the anatomy and physiology of the inner ear and the development of clinical methods to observe and record eye movements have enhanced our ability to perform a comprehensive office neurotologic examination of the hearing and balance organs[7,8]. Ear examination should be conducted using a microscope and tuning forks, especially ears with trauma or prior surgeries.

The vestibular system examination should include neck movements, eye movements and vestibular responses; namely the VOR, VSR and VVOR. Neck is examined for full range of motion and flexibility in all directions to determine primary and secondary causes of limited and guarded neck movements. Office-based VNG is used to observe and record normal and abnormal eye movements commonly associated with VOR abnormalities. Furthermore, subtle eye movements of incomplete vestibular compensation and those associated with the superior canal dehiscence syndrome have been easier to observe and record. Critical to the accurate interpretation of VNG is the familiarity with the semicircular canal innervations of the extraocular muscles.

VOR examination includes spontaneous nystagmus, vestibular head rotation nystagmus, post head-shaking, positional nystagmus exams and BPPV nystagmus. Vestibular per-rotatory nystagmus intensity and symmetry can be observed or recorded to assess reduced unilateral and bilateral vestibular functions in the horizontal and vertical directions. The presence of post head-shaking nystagmus or ocular drift (without nystagmus) indicates an uncompensated peripheral unilateral vestibular dysfunction.

Dix-Hallpike examination is essential to determine the side, the involved canal, and the underlying mechanism in BPPV. Although not frequently stated in the literature, the Dix-Hallpike exam stimulates the posterior and horizontal canals on the down side and the anterior canal on the up side. Furthermore, BPPV can be due to cupulolithiasis (otoconia adherent to the cupula) or canalithiasis (otoconia floating in the endolymph). With the aid of VNG, the canal, or canals, and the mechanism of BPPV can be determined. This is critical because the treatment is different for each canal and for each mechanism. The Semont maneuver is effective in treating posterior canal cupulolithiasis and the Epley maneuver for posterior canal canalithiasis[9,10]. The Lempert maneuver is used for treating horizontal canal canalithiasis and the Hamid maneuver is used for horizontal canal cupulolithiasis[11,12].

The office exam of VSR includes traditional stance, gait, and stepping tests can be used. The use of a high compliant foam pads to observe postural stability and reflexes with eyes open and eyes closed have been used to further "stress" and challenge the posture system.

In my experience, active head-shake while standing on a high compliant foam pad is the most challenging part of the exam. Findings of increased postural sway, inappropriate sway strategy at the limits of stability and post stepping drift are helpful for abnormal VSR. The neurotologic exam should also include examination of the cranial nerves, motor and sensory modalities. The cerebellar exam should include visual suppression of vestibular nystagmus during active head rotation.

Auditory and Vestibular testing: what to order and when?

Patients with hearing and or vestibular disorders should get comprehensive audiometry (air and bone thresholds and speech discrimination) and Tympanometry. Additional tests such as OAE , ABR and ECoG should be obtained as clinically indicated. The time-honored electronystagmography (ENG) vestibular test remains the most frequently utilized test worldwide. Rotating chair and dynamic posturography are less frequently used.

Several observations can be drawn from a large database of patients since 1980[13]. First, over interpretation of the ENG results, especially the oculomotor test results, which frequently leads to unnecessary neurological investigations and magnetic resonance imaging (MRI) studies? The yield of "central eye movement abnormalities" is very low and therefore, it is advisable for ENG readers, especially the new ones, to interpret eye movements cautiously. It is not inappropriate to read ENG oculomotor tests as normal for several years while "storing" their pattern for more accurate interpretation with increased experience. Most abnormal eye movements that are of clinical significance can be seen during a thorough neurotologic exam. Second, ENG raw tracings must be viewed and evaluated instead of solely relying on "computerized" results which can be due to noisy raw data as opposed to true nystagmus signal. Third, care must be taken when interpreting caloric test results to accurately determine true vs. relative unilateral vestibular hypofunction and to avoid missing true bilateral reduced caloric responses[13].

It is also important to recognize that ice-cold irrigation in the supine position is not a maximum stimulation of the vestibular nerve. The reason is that in the supine position, cold irrigation leads to canal inhibition and a reduction in the vestibular resting neural activities from 100 spikes/sec to zero. In the prone position, cold irrigation leads to canal stimulation and increases the vestibular nerve resting discharge from 100 to 400 spikes/sec, which is three times greater than that of the neural signal in the supine position. Another important point is that the caloric response is a low-frequency response of the VOR and absent caloric responses do not imply total vestibular function loss[14].

Rotating chair and/or active head rotation are useful in testing the high frequency VOR (up to 5 Hz), determining the degree of residual vestibular, slow-phase asymmetry and phase shift. The active head rotation test

is more practical in determining the VOR residual gain when ice caloric responses are absent and the history is positive for severe vestibular loss (i.e. evident oscillopsia). The phase and asymmetry from the active head rotation test are of limited clinical value.

Dynamic posturography test is comprised of sensory and motor components. The sensory test gained wider acceptance and is useful in functional assessment of balance and in tailoring vestibular rehabilitation programs. The sensory test is also helpful in detecting "aphysiologic" sway patterns especially in medical legal cases. The motor test is less utilized and its clinical yield is low in peripheral vestibular dysfunction.

A relatively new vestibular test is VEMP. It is gaining more acceptance and importance as a test of the saccular-inferior vestibular nerve pathway. These are sound evoked potentials (normally at or above 100dbHL) that are recorded from the sternocledomastoid muscle using surface electrodes (very much like ABR recordings). The signal is a robust and a repeatable peak and valley at 13 and 23 msec post stimulus time. VEMP is particularly helpful in cases of superior canal dehiscence, Tumarkin's crisis, or symptomatic large cochlear aqueducts.

Finally, it is critical to emphasize that auditory and vestibular tests are electrophysiologic functional tests that do not lead to a specific diagnosis of the underlying disease. For example, a unilateral hearing and vestibular loss can be due to an acoustic tumor, Menière's disease, vestibular neuritis or Migraine. These tests are part of the comprehensive medical evaluation needed to establish the diagnosis and treatment.

Newly recognized disorders

Autoimmune inner ear disease (AIED), superior and less common posterior semicircular canal dehiscence and vestibular migraine are "newly" recognized entities in neurotology. AIED is defined as bilateral, asymmetric, rapidly progressive (over days or weeks) sensorineural hearing loss, aural fullness, tinnitus with or without vertigo[15,16]. The presentation is similar to bilateral Meniere's disease and is common in patients with other AIED. Despite several attempts to identify specific laboratory patterns and markers, the corner stone for diagnosing this entity remains the clinical presentation and respond to aggressive use of oral and or intratympanic steroids. Other autoimmune medications like Methotrexate and Enbril have also been used[17]. Responses are variable but most patients can be brought under control with prompt treatments and use of hearing aids.

Dehiscence of the superior canal is a congenital defect in the eminence of the temporal bone. The clinical picture is often subtle and most patients present with persistent motion intolerance and visual symptoms with loud sounds and pressure changes[18]. Neurotologic exam typically shows bone conduction hypersensitivity, down beat nystagmus or "jumping eye movements" to loud sounds or tragal compression. Audiometric findings show low-frequency conductive hearing loss similar to Otosclerosis but with intact ipsilateral acoustic reflexes. ECoG, with TM electrode, is usually positive with the SP/AP ratio greater than 0.5. VEMP at lower sound thresholds (< 80dbHL). ENG is not usually helpful. A high resolution CT scan of the temporal bone confirms the presence of the dehiscence. Coronal sections may not be sensitive enough especially with standard cuts. Treatment can be medical (acetazolamide, topiramate), PE tube (with pressure-induced symptoms), or surgical closure of the bony defect via a middle fossa or transmastoid approach.

The differentiation between migraine and Menière's can be challenging because migraine can mimic typical Menière's disease, with fluctuating low-frequency hearing loss, tinnitus, and vertigo[19]. A careful history of past headaches, a family history of headaches, migraine trigger factors precipitating dizziness and non-headache migraine symptoms during dizziness (photophobia, phonophobia, and focal neurologic symptoms) are very important to elicit. Most of these patients have had migraine, "sinus" headache and or a strong family history of migraine. The history, neurotologic exam, basic audiometry, and brain imaging (when indicated) are sufficient to make the diagnosis of migraine vertigo.

The association of headaches with vertigo is typical of migraine, but is not present in all patients. In my experience, migraine dizziness is mostly motion sensitivity as opposed to true vertigo and is not associated with severe fluctuating low-frequency hearing loss.

The treatment of migraine is multidimensional and includes modifying life style, diet, avoiding triggers, and use of abortive and prophylactic medications. The triptan class of medications remains the most effective in aborting severe Migraine episodes. Topiramate (a carbonic anhydraze inhibitor) has been effective in prophylactic treatment of vestibular migraine. It is advisable to start at a low dose at bed time (25 mg) and gradullay increase the dose according to clinic response. Most patients respond well to 50 or 75 mg dosing. Other medications such as beta blockers, antidepressants, NSAIDS can be used to optimize migraine treatment. It is important to have patients keep diaries of their symptoms for review and adjusting or changing medication.

Intratympanic perfusion for Menière's disease and immune inner ear disease

The pathology of Menière's disease is frequently "idiopathic" endolymphatic hydrops[20]. AIED is similar to Menière's, but has a more rapid course affecting both ears. Recent data support an ionic imbalance of the endolymph as the final common pathway to endolymphatic hydrops and suggest that steroids improve and restore normal stria vascularis function by increasing Na+ transport and expression of active water channels (aquaporins) in the endolymph surrounding tissues.

Several clinical studies on the use of intratympanic steroids to treat Menière's disease and sudden sensory neural hearing loss have produced variable long and short term results. There are no consensuses among users and several reasons for that.

First, the dose and the type of steroids used show a wide variation. Steroid doses ranged from 4 mg/ml to 24 mg/ml (dexamethasone) or 40 mg/ml (methylprednisolone). While the advantage of intratympanic perfusion is to deliver a higher concentration to the inner ear, it appears for most studies that the dose was dependent on what was available in the market instead of the maximum dexamethasone dose of 24 mg/ml. The most common type of steroid used has been methylprednisolone, based on an animal study that favored methylprednisolone relative to dexamethasone because it yielded "higher concentrations" in the perilymph and endolymph after intratympanic injections[21]. Although this study provided relevant information regarding the pharmacokinetics of different steroids, my re-evaluation of the results showed that dexamethasone is more efficacious. The study clearly showed that absorption of dexamethasone into the stria vascularis was faster than methylprednisolone, which remained in the endolymph longer than dexamethasone by a factor of 4 to 6 hours. It is known that steroids act intracellularly within the stria and surrounding tissues after being passively or actively endocytosed. Thus, the presence of high methylprednisolone concentrations in the endolymph reflects its lower absorption by the stria making dexamethasone more efficacious for intratympanic perfusions. Unfortunately, dexamethasone 24 mg/ml was removed from the market in the late 2000 and can now only be produced as a compound.

The second reason underlies the variability of ITPs results is the disease stage at the time of perfusion. Our experience has been that perfusion should be performed at an early stage of the disease before, supposedly, the stria has not undergone permanent damage. High concentration of dexamethasone has the best chance of controlling Menière's disease at an early stage, at which point the cochlea is still amenable to the positive effects of steroids on the stria and its ionic homeostasis with surrounding structures.

Intratympanic gentamicin perfusion has long been used and accepted as a treatment for Menière's disease on the basis that it reduces the production of endolymph by the vestibular dark cells and destroys the remaining "non-functioning" vestibular sensory epithelia[22-24]. Gentamicin is effective in controlling vertigo in the late stage of the disease when hearing loss has already become severe. However, it is associated with significant hearing losses (10-30%) if used at early stages of the disease. The use of gentamicin and steroids has reduced the number of surgical operations for vertigo over the past decade[25]. Gentamicin was also found to be effective in treating drop attacks in Menière's disease.

Another important issue with intratympanic treatments is the need for randomized controlled studies (RCT). Although we all would like seeing the results of long-term controlled studies in medicine, this may have significant economical and ethical drawbacks. These RTC studies may indeed be justified for new, experimental, and expensive treatments that have significant morbidity, for example, cancer treatments. The natural history of Menière's disease is well-documented and can actually serve as a benchmark against which treatments can be judged. The side effects of intratympanic steroids and gentamicin are minimal. A successful outcome is achieved in about 90% of cases, with treatment at an early stage (steroids) or late (gentamicin), which far exceeds the placebo effect of about 30%[26-30].

Gentamicin perfusion has been used since 70's and clinical experience has validated its use even without the need for further "randomized" trails. The basic science and clinical applications concerning gentamicin and steroids are so established that, in my opinion, it is difficult to justify withholding active reserving this treatment for more than two years , especially that steroid treatment for early Menière's disease is associated with significant hearing gain and vertigo control. It is important to state here that intratympanic steroids treatment is indicated for active Menière's disease or hydropic changes of the inner ear. It is contraindicated for other forms of hearing loss or dizziness.

The specialty and practice of Auditory and Vestibular Medicine

Otolaryngologists and audiologists are facing a new challenge in defining the role of physicians (medicine) and audiologists (science) in the management of patients with hearing and balance diseases or disorders. Unfortunately, both professions are trying to resolve this new challenge independently, ignoring the fact that these two professions have been intertwined historically and are inseparable.

The new challenge lies in the fact that audiologists are spending their time and energy gaining independence, whereas otolaryngologists are trying to create alternative solutions to providing audiometric and vestibular testing to their patients. Having traveled the journey from auditory and vestibular science (my EE, audiology, and PhD training) to becoming a physician specializing in medical otology and neurotology, I believe that these efforts are futile. They are bound to compromise the quality of needed care for our patients.

During my audiology and vestibular science training, I learned the detailed anatomy and physiology of these systems to understand how they work and how to test their function. I learned about hearing aids and auditory

rehabilitation. What I did not learn during my science training is the anatomy and physiology of the rest of the body, clinical sciences, the mechanisms of health and disease, or how to care for sick patients. Indeed my non medical training was limited in allowing me to make a clinical diagnosis, determine the underlying etiology, or provide a specific treatment. These limitations were blurred in my own mind, and I quickly realized that I must complete my medical education to provide medical audiologic and vestibular care to my patients.

Ears Nose Throat (ENT) residency training programs are surgically oriented. Because of the complexity of head and neck anatomy, physiology, and diseases, residents have limited time to acquire the auditory and vestibular knowledge that science training offers. Most ENT training programs include basic audiology, speech, and vestibular testing however, most residents devote more time to surgery and care of sick patients. This focus is appropriate, because ENT residents choose the specialty to become surgeons; however, they quickly realize that most hearing and balance diseases are not amenable to surgical treatments.

Several countries have developed training programs for Auditory and Vestibular medicine physicians while other countries have relied on audiological science training programs. Each of these models has their pros and cons. Historically, audiological scientists' provided hearing testing and auditory rehabilitation and were working side by side with ENT physicians. Auditory and vestibular physicians had more clinical involvements by virtue of their medical training. This codependent model ensured appropriate care to most of patients; however, it was bound to reach the crossroads that it is now facing. The current state of affairs is rather disappointing. In the USA, audiologists who are not medically trained are trying to gain independence and become "independent providers" to care for hearing and balance patients.

The recent invention of the "Doctor of Audiology AuD" has propelled them to market aggressively as the profession "trained and qualified to diagnose and treat hearing and balance disorders".

In Europe, the health care economy forced the powers to push for using "paramedics" to provide direct care for these patients. In the Middle East, Auditory and Vestibular physicians are practicing Otology and NeurOtology despite the fact that their training was modeled after that of radiologists and pathologists. In all of these scenarios, patients with hearing and balance diseases ended up with fragmented and more expensive care. I am hoping that the current efforts by otolaryngologists and audiologists can be redirected to accept and nourish the inherent differences between audiologic medicine and audiologic science.

There are excellent audiology MSc and PhD programs that have been, and still are, graduating competent audiologic scientists who are critical in supporting clinical and research areas of hearing and vestibular sciences.

Ears Nose Throat training programs should place more emphasis on audiologic and vestibular medicine. Ideally, the audiologic physician (medical neurotologist) model should be developed within the ENT profession.

Finally, it is important that audiologists and otolaryngologists realize the inherent differences and limitations of their respective trainings. We must work together to educate our patients, the public, and insurance companies to ensure delivering the best possible care to patients with hearing and vestibular diseases. We must face the new challenge with open minds and spirits to forget our differences and build on our tradition of collaboration.

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