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Diagnosis and follow-up of patients suffering from vertigo

Ph.D. thesis

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List of abbreviations

AAO-HNS	American Academy of Otolaryngology - Head and Neck Surgery
AUC	area under curve
AVS	acute vestibular syndrome
BERA	brainstem evoked response audiometry
BPPV	benign paroxysmal positional vertigo
CP%	canal paresis
CSR	cervicospinal reflex
CT	computer tomography scan
CVD	central vestibular disorders
CVT	caloric vestibular test
DHI	dizziness handicap inventory
DP%	directional preponderance
dPTA	interaural difference of hearing level
E	emotional question
ED	emergency department
EHC	eye-head cell
ENG	electronystagmography
ENT	ear, nose, throat specialization
EOM	extraocular muscles
F	functional question
GP	general practitioner
HINTS+	head impulse, nystagmus, test of skew, hearing loss
i-BPPV	idiopathic BPPV
IT	intratympanic treatment
ITS	intratympanic steroid
IVN	inferior vestibular nucleus
LVN	lateral vestibular nucleus
MD	Ménière’s disease

MRI	magnetic resonance imaging
MVN	medial vestibular nucleus
P	physical question
PC	personal computer
PTA	pure tone audiometry
PVD	peripheral vestibular disorders
PVP	position-vestibular-pause neurons
QoL	quality of life
ROC	receiver operating characteristic curve
s-BPPV	secondary BPPV
SD	standard deviation
SVN	superior vestibular nucleus
TIA	transient ischemic attack
TNR	true negative rate
TPR	true positive rate
US-COMP-CCG	ultrasound-computer-craniocorpography
vHIT	video-head impulse test
VO	vestibular-only neurons
VCR	vestibulocollic reflex
VOR	vestibuloocular reflex
VSR	vestibulospinal reflex

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1. Introduction

Vertigo and dizziness are multisensory syndromes that are often confronted in the daily practice.

The manifestation of peripheral either central vestibular disorders is determined by how the vestibular system is operating: the individual's perception of motion and body position, gait, ocular motor control, and spatial orientation, whereas are all considered. These complaints can be of a problematic presentation, both from a diagnostic and a management standpoint, needing a multidisciplinary approach, patient understanding and time.

Vertiginous causes may include vestibular and extravestibular systems. Among each system, gait problems exists and acute manifestation of it combined with vertigo is a priority to be solved.

Vestibular disorders can be divided into peripheral and central causes. Peripheral vestibular disorders (PVD) can be differentiated by their symptoms, 1) acute/subacute unilateral failure of vestibular function, 2) paroxysmal, insufficient stimulation or inhibition of the peripheral vestibular system and 3) chronic peripheral loss of vestibular function. Among the frequent forms of PVD are the benign paroxysmal positional vertigo (BPPV), and Ménière's disease (MD).

Central vestibular disorders (CVD) are affecting the pons, medulla, or cerebellum, consequently causing vertigo, vegetative symptoms, severe ataxia, multidirectional nystagmus that is not suppressed by optic fixation, and other neurologic signs. Extravestibular causes of vertigo include neurological, cardiovascular, metabolic, psychogenic, rheumatologic and visual problems.

Patients suffering of acute vertigo and instability of gait and posture; based on the statistics collected, will firstly visit the Emergency Department (ED) and from there a diagnosis and recommendation for further examination, if it is needed, will be given.

Along with vertigo, vestibular ataxia - imbalance may appear which is related to an inappropriate activation of the polysynaptic vestibulospinal pathways. Imbalance has the capability, in a short and/or long term to deteriorate the quality of life (QoL), since it interacts with the daily tasks needed to be fulfilled as well as with desired social tasks.

Due to this simple seeming complaint, a non-invasive diagnostic equipment was developed to examine the balance system, based on the statokinetic tests and vestibulospinal reflex (VSR), which takes no more than few minutes (approximately 5 minutes), and is known under the name of ultrasound-computer-craniocorpography (US-COMP-CCG).

In view of this, it may be worthy to examine the correlation between the gait system and the vertiginous system causing the complaints. Therefore, by approaching this matter in a more complex and complete way, we are able to provide proper diagnosis, with proper guidance to the individual suffering from it and give the opportunity to continue completing and participating in daily tasks successfully, and therefore maintaining a better QoL.

1.1. The vestibular system

To maintain a normal movement and equilibrium the vestibular system is essential. It is capable of detecting movements of the head in space and orientation, and therefore reflexes are generated that are needed for our everyday actions, such as maintaining an upright posture and stabilizing the visual axis. Consequently, our sense of movement and orientation is provided by the vestibular system [1].

The organs involved in the system are in proximity with the auditory sensory organ, an important fact, since it explains the correlations of some vestibular disorders with cochlear symptoms.

1.1.1. Peripheral vestibular system

It is composed of two types of sensors: the saccule and utricle (two otolith organs) which detect the linear acceleration, as well as the three semicircular canals, which detect angular acceleration in three axes (2 horizontal and 4 vertical canals) [2]. The three semicircular canals are designed based on their position and are set out in three orthogonal planes (Figure 1.). A circular path of fluid continuity compromises each canal, interrupted at the ampulla by the cupula. The cupula is pushed by the fluid movement, which accommodates the hair cells that transduce the mechanical movement

to electrical signals. The stimulus produced on the semicircular canals is the angular acceleration, and the neural output from the sensory cells constitutes the velocity of rotation [3].

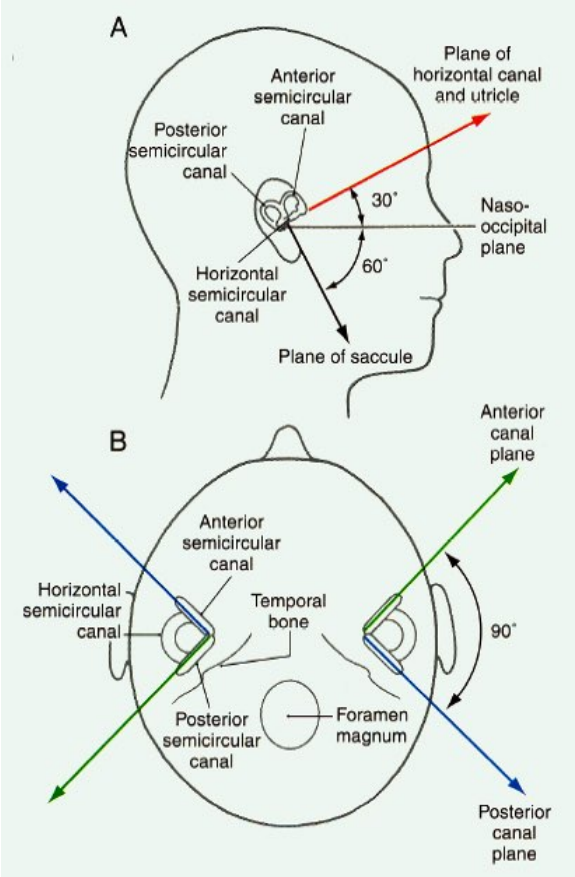

Figure 1. Orientation of the vestibular receptors. In the lateral view (**A**), the horizontal semicircular canal and the utricle lie in a plane that is tilted relative to the nasooccipital plane. In the axial view (**B**), the vertical semicircular canals lie at right angles to each other (https://neupsykey.com/the-vestibular-system-4/).

The saccule and utricle, are capable of detecting the linear acceleration. Therefore, responding to linear gravitational forces, they are also known as gravity receptors. The hair cells consist the sensory epithelium that, in their order will tonically release a transmitter, aiming in spontaneous activity of vestibular nerve fibers. Cilia are emerging from the hair cells and are rooted in a gelatinous matrix containing $CaCO_3$ crystals. Due to inertia and in regards to linear acceleration, the crystals are left behind.

The resultant bending of cilia causes excitation or inhibition of hair cells. The otolith organs due to acceleration sensitivity, are capable to detect the gravity, in addition to transient linear acceleration attributed to movement [4, 5, 6].

Body stabilization and the ocular system can be impaired when damage to the otoliths or their central connections occur [7]. Vestibular disorder associated with the impaired otolithic organs is the BPPV.

The membranous labyrinth encloses endolymph in a hollow system, which this passes via the endolymphatic duct to end up in the endolymphatic blind sac. The perilymphatic system forms a hollow space consisting of the scala tympani and the scala vestibuli. Perilymph separates the membranous labyrinth from the internal layer of the labyrinthine capsule, and is considered the immediate substrate of the cochlear and the vestibular sensory cells. Endolymph is a filtrate of the perilymph that has completely different concentrations of sodium and potassium, which are kept constant by the means of the epithelium of the stria vascularis. The regulation of volume of the fluid circulating in the endolymphatic system is done by the electrolyte composition of the endolymph. The basis of the electrolyte exchange system is the cellular potassium-sodium exchange pump found in stria vascularis, the utricle and the saccule. In addition, there is a passive diffusion between the endolymphatic and perilymphatic spaces, with potassium-sodium ion exchange in the endolymphatic sac. Functional disturbance of this system leads to MD [8], whereas authors suggested that due to the obstruction of the endolymphatic sac, production of hormones (e.g. saccin) may take place, increasing the production of endolymph and preventing the obstruction. Glycoproteins may also be produced by the sac, that osmotically attract endolymph towards it. Consequently, overflow of endolymph behind the obstruction is produced, the obstruction might be eased and the sudden outflow change across the sac could trigger vertigo attacks [9, 10].

The labyrinth produces vestibular signals, that are therefore transferred to the vestibular nuclei (VN) by the means of the vestibular nerve fibres, which end to the neural structures that control eye movements, posture, and balance. In the VN most neurons receive inputs from the semicircular canals and the otolith organs. By this mean, neurons are capable of encoding rotations, and capable of responding to linear

accelerations of motion counting the constant influence of gravity. The otolith organs, therefore and the otolith afferents are not able to distinguish accelerations due to head tilt from translational self-motion [11]. Therefore, convergence of signals from the semicircular canals and otoliths in the VN, fastigial nucleus of the cerebellum, and Purkinje cells in the cortex of nodulus and uvula of the cerebellum provides a way to solve this specific problem. While encoding of the inertial motion is done by the nodulus-uvula Purkinje cells, the firing rate of neurons of the VN and fastigial nucleus provides a combination of responses [12]. Consequently, for a movement to be accomplished, sensory information from somatosensory, vestibular and visual systems needs to be fused based on the goal of action asked. In order to stabilize gaze and ensure clear vision during everyday actions, the vestibuloocular reflex (VOR) adapts in response.

Another critical role of the vestibular system in ensuring postural equilibrium is by producing necessary adjustments during both self generated movements and externally applied influences.

1.1.2. Central vestibular processing

Four main nuclei are included in the vestibular complex: the medial vestibular nucleus (MVN - Schwalbe’s nucleus), the superior vestibular nucleus (SVN - Bechterew's nucleus), the lateral vestibular nucleus (LVN - Deiters's nucleus), and the inferior/or descending vestibular nucleus (IVN - Roller’s nucleus), along with some other subgroups [13]. Even so no true segregation of inputs from afferent neurons exists, the Schwalbe’s and Bechterew's nucleus receive inputs respectively mainly from the horizontal and vertical semicircular canals. Utricular afferents terminate mostly in the Roller’s nucleus, where they also send projections to the Deiters, Schwalbe, and Bechterew's nucleus. Saccule fibers mainly innervate the Deiters’s and Roller’s nucleus. Additionally to these projections from vestibular afferents, the VN neurons also collect inputs from cortical, cerebellar, and other brainstem structures (Figure 2.). Which in turn, these latter mentioned inputs pass on somatosensory, visual inputs and signals linked to eye movements and premotor head movement orders to the VN. As a result,

these extravestibular inputs change the processing of vestibular information at an early stage of sensory processing.

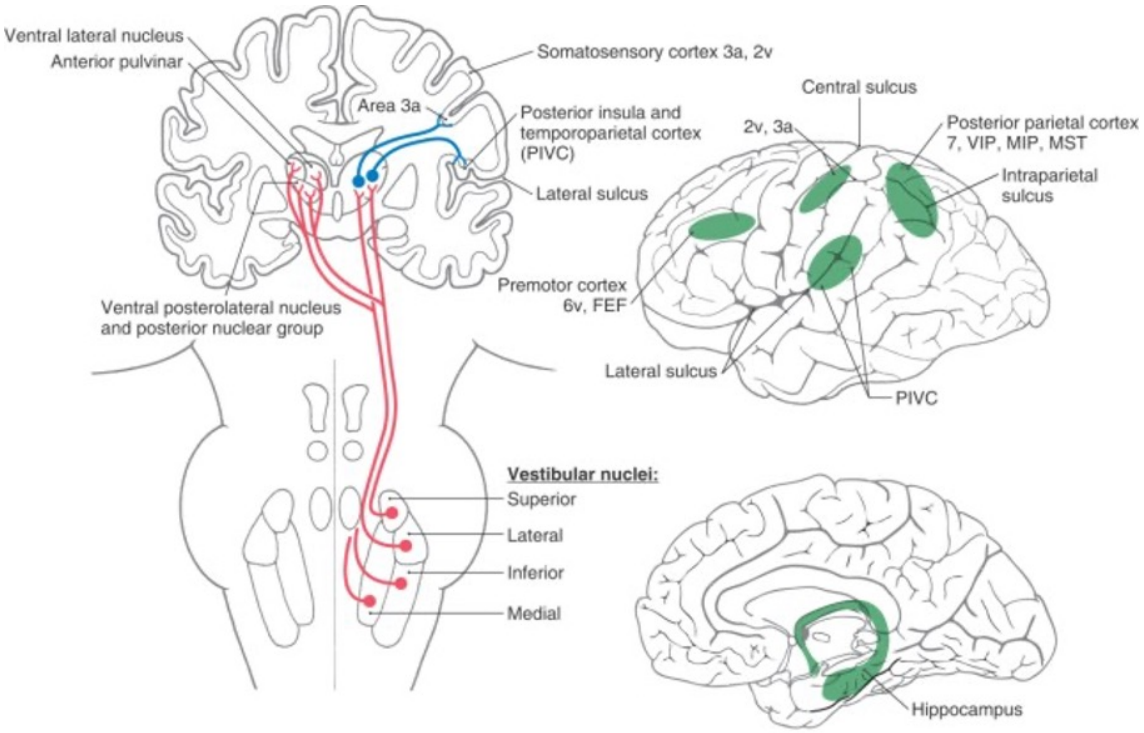

Figure 2. VN inputs (https://clinicalgate.com/the-vestibular-system/).

1.1.3. Vestibular projection pathways

The cerebellum consists of five main regions. These include 1) the nodulus and ventral uvula, 2) the flocculus and ventral paraflocculus, 3) the oculomotor vermis of posterior lobe, 4) I-V lobules of the anterior lobe, and 5) the deep cerebellar nuclei.

The VN are interconnected with the nodulus-uvula of the cerebellum, whereas these areas allow to the computation of inertial motion [14]. The flocculus and adjoining paraflocculus are entangled in the formation and the plasticity of compensatory eye movements, that include the optokinetic reflex and smooth pursuit, as well as the VOR [15, 16]. Neurons in the oculomotor vermis, which includes the lobules VI and VII of the vermis, bequest to visual-vestibular processing [17]. This cerebellar region from the nucleus prepositus also acquires eye movement signals [18] along with pursuit-related inputs from the dorsolateral pontine nuclei [19]. The lobules I-V, conceal both vestibular

and neck proprioceptive-related signals [20] and is considered to control the VSR. The integration of vestibular and proprioceptive information guarantees that the motor responses generated by these reflexes are suitable to maintain body stability. The signal processing done in the fastigial nucleus is linked to the vestibular system. Therefore, primary and secondary vestibular inputs are received, along with input from the cerebellar vermis. Consequently, a critical role is played by the fastigial nucleus in the production of orienting behaviors and postural reflexes, and correspondingly projects to brainstem structures that regulate these behaviors including the VN and medial reticular formation. Numerous neurons in this area merge vestibular and proprioceptive inputs, and consequently encode vestibular signals in a body-centered reference frame [12].

1.1.4. The Vestibuloocular Reflex (VOR)

The VOR generates compensatory eye movements of equal and opposite magnitude to head rotations to present a clear image on the central fovea, whereas this is in relativeness to space. The VOR has been discovered by Endre Hőgyes in 1881 [21] and is probably our fastest behavior; in correspondence to head movement, whereas eye movements are produced with a latency of only 5-6 ms [22]. Therefore, a faster gaze stabilisation is possible compared to the most rapid visually evoked eye movements. During daily actions such as active head turns, the motion of the head can have frequency content close to 20 Hz [23]. The VOR, moreover, can have a remarkably compensatory gain and a minimal phase lag over the physiological relevant range of head movements [24]. Consequently, the VOR is compensatory for head movements in everyday life.

The VOR produced by head rotation is moderated by the so-called three-neuron arc and was firstly mentioned in 1933 by Lorente de No'. It is made up of projections from vestibular afferents to neurons in the VN, which successively project to extraocular motoneurons. This latter mentioned arc simplicity is reflected upon VORs‘ fast response time; where compensatory eye movements lag head movements by only 5-6 ms [22]. Firstly, the transmission of driven information from the vestibular end organ is suppressed when the visual axis of gaze is redirected by using combined eye-

head orienting movements [25]. Secondly, the primary neurons, within the VN, that are responsible to mediate the direct VOR pathway are the so called position-vestibular-pause (PVP) neurons. Therefore, they respond to head motion and encode eye position signals, as well as pause during saccades. The differences in responses of the PVP neurons are consistent with these distance-related changes in VOR gain [26]. Eye-head cell (EHC), is a second class of neurons contributing to driving the responses of VOR eye movement, with the ability of calibrating the VOR during conditions when the amount by which the eyes must rotate to counter head motion to preserve stable gaze is altered.

1.1.5. The Vestibulospinal Reflexes (VSR)

The VSR plays an important role to maintain the head in an upright position by coordinating head and neck movement with the trunk and body. Similar to the VOR, the most direct pathways moderating the VSR comprise three neurons: vestibular afferents project to neurons in the VN, which therefore project to spinal motoneurons [27].

For VSR, two functional categories can be acclaimed: the ones acting on the neck muscles (vestibulocollic reflexes - VCR) that stabilize the position of head in space and the ones acting on the limb muscles that consequently stabilize the position of the trunk in space [28]. In consequence, head and trunk stabilization are two postural actions that are pursued simultaneously [29]. VSR are also tightly associated to the cervicospinal reflex (CSR), whereas activations of trunk muscles elicited by stimulation of neck receptors following rotation of the head respectively to the trunk. As a result, VSR and CSR acting on the limbs interacts, and so they change the postural tone only when the position of the trunk in space is altered [28, 30]. Property of VSR and CSR is their high degree of spatial organization. Each and every muscle is triggered for a given direction of the stimulus, so that a head-to-body displacement will produce a pattern of muscle activation that depends critically upon the plane of rotation [31, 32]. Nevertheless, VSR afferentation could be influenced by muscle and joint disorders, and increasing the differential diagnostic difficulties in the balance disorders. VSR, can be evoked by electrical stimulation of the labyrinth registered to the mastoid bone.

Cathodic current registered on one side surges the discharge of the corresponding labyrinthine afferents and when the subject is facing forward, it generates a body sway in the frontal plane, directed away from the stimulated labyrinth [33].

Other studies have highlighted the importance of extravestibular signals in shaping the sensorimotor transformations that mediate the VSR [34, 35]. Neurons that are sensitive to vertical rotations have been documented primarily in the Bechterew and Schwalbe's nucleus [36, 37]. In both the horizontal and vertical systems, the rotationally sensitive neurons can be categorized into 3 main classes based on their feedbacks to voluntary eye movements and passive whole-body rotations. These include 1) PVP neurons, 2) vestibular-only (VO) neurons, and 3) EHC. While vestibular afferents exhibited no differences in sensitivity [38] or firing rate variability [39] during active movements, VO neurons express striking differences in the two conditions [40]. More precisely, VO neurons respond to passive head movements but throughout active head movements their responses are markedly attenuated (70%). Given that these neurons project into VSR pathways, has led to the proposal that the VCR is turned off throughout voluntary head movements [41]. The mechanism accountable for the selective cancellation of neuronal responses to active head motion is exclusively produced in conditions where the activation of neck proprioceptors matches the motor-generated expectation.

Vestibular reflexes such as the VCR and VSR are important for preserving head and body posture in our daily tasks. They function to stabilize the head relative to inertial space by ordering the head to move in the contrast direction to that of the current head-in-space velocity. The VO neurons that are located in the VN project to the cervical spinal cord and are considered to mediate the vestibulocollic pathway [42] and likely to control the VSR.

Consequently, the movement and body position receive information from the VN. These signals go down to the forebrain and perceive the orientation, to the spinal cord and cerebellum for the postural control and down to the oculomotor system for the eye movements (Figure 3.).

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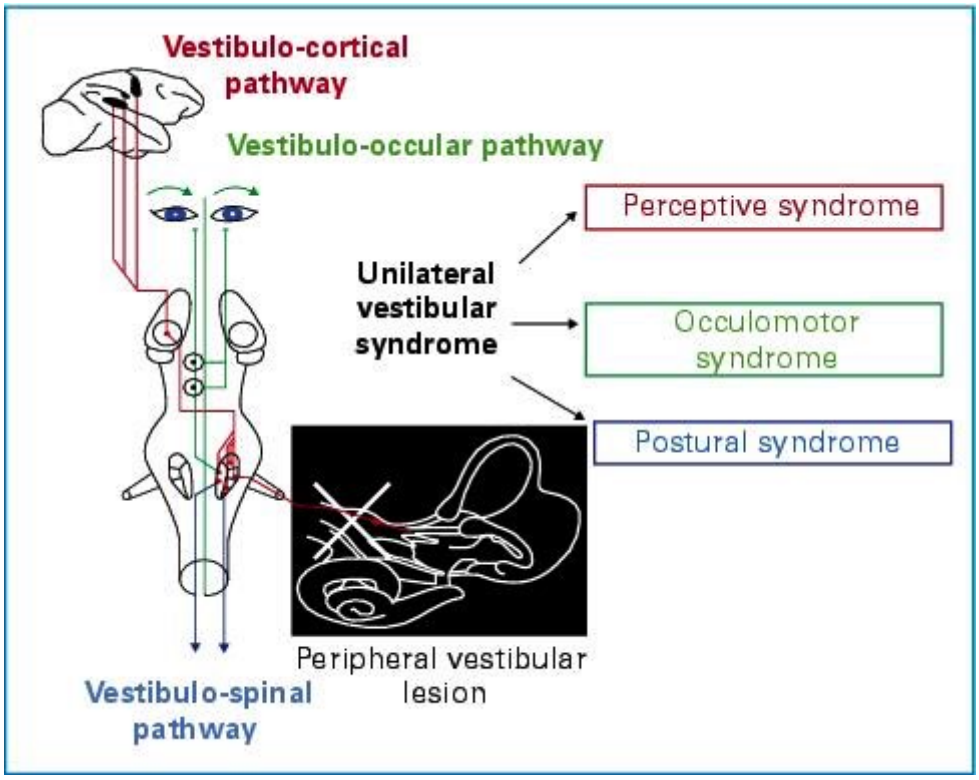

Figure 3. Diagram of anatomo-physiological organization of vestibular system and vestibular syndrome after peripheral vestibular lesion. Central projections of peripheral labyrinthic afferents and main vestibular pathways involved in postural control (vestibulospinal pathway), oculomotricity (vestibuloocular pathway) and perception of body orientation (vestibulocortical pathway). A unilateral vestibular lesion results in postural, oculomotor and perceptive impairments (https://www.jle.com/fr/revues/age/e-docs/locomotion_and_spatial_navigation_in_vestibular_pathology_282681/article.phtml).

1.2. Ultrasound-Computer-Craniocorpography (US-COMP-CCG)

Craniocorpography was originally designed as a non-electronic, simple office recording procedure for head and body movements. US-COMP-CCG means the objective examination of VSR using ultrasound, and the procedure combines a standing test (Romberg) with a stepping test (Unterberger-Fukuda) [43]. Based on a positioning system and the existing ultrasound markers on the equipment (Figure 4.), a very precise localization of the patient is possible. The registration of the movements is saved in the

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personal computer (PC) which withholds a radar-like registration program with the ultrasound markers analysis. The first two ultrasound markers are located on the helmet that the patient is carrying, and another set is located on each shoulder fixation of the equipment (Figure 5.).

Based on our installation, above the patient (Figure 5.), the ultrasound receiver unit is stationed containing several ultrasound microphones, whereas the data processors are receiving the sound traces from the head and from the shoulders. The signals received are triggered by and sent via the computer unit.

Figure 4. Representation of the US-COMP-CCG (https://www.aemedi.es/documentos/CCG-GB_72.pdf).

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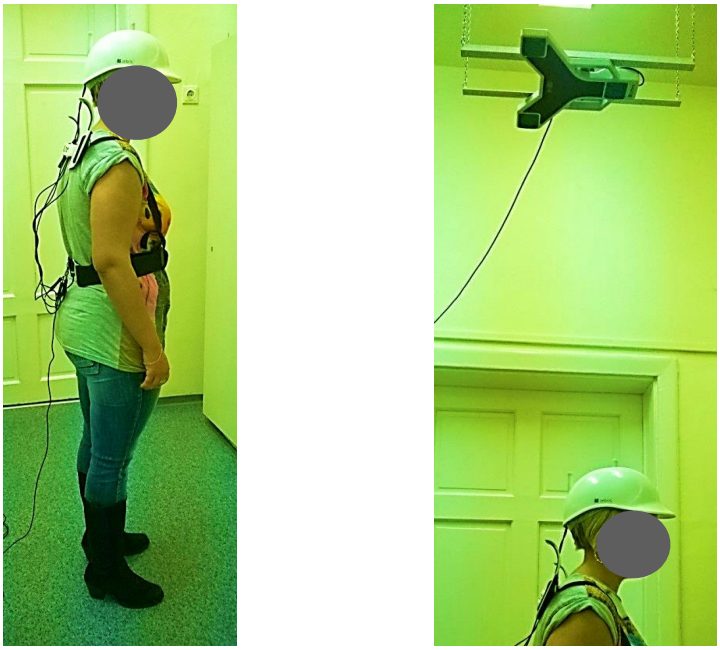

Figure 5. Representation of the US-COMP-CCG appliance on a patient [44].

The computer unit, therefore, calculates the spatial position of all four ultrasound markers, whereas the PC software shows the results obtained in each test. The markers are represented on the PC monitor schematically with different colors: anterior marker is blue, posterior marker is orange, left localized shoulder marker is red and right shoulder marker is green (Figure 6, 7.). Using those ultrasound markers on head and shoulders, the craniocorpograph automatically measures and displays the number of steps and the movements of the head as compared with the shoulder movements, assessed by the head torsion and head nod angles [45]. Schematic graph is created, with two axis: X and Y. Therefore, it measures and analyzes the numerical data of vestibulospinal tests of the patients suffering from vertigo and/or balance disorders [46, 47].

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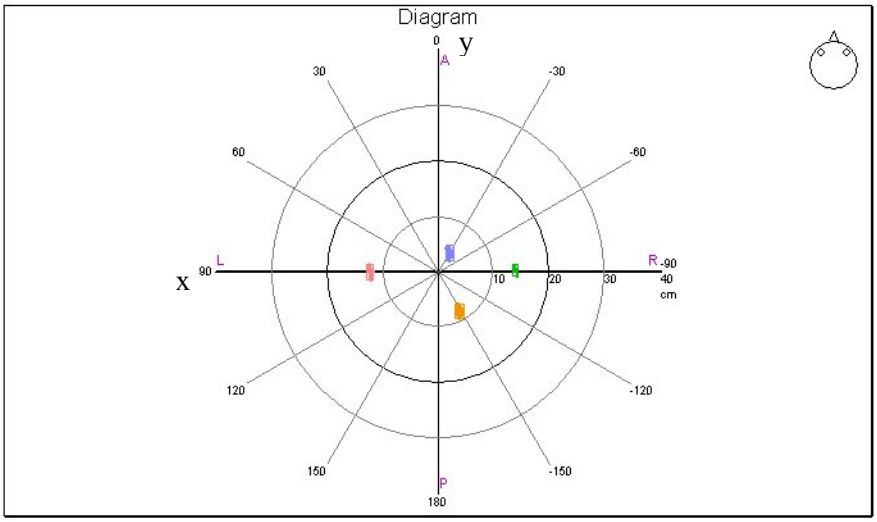

Figure 6. Representation of the sensor's registration on the PC monitor during Standing test. (Figure taken from our clinical material).

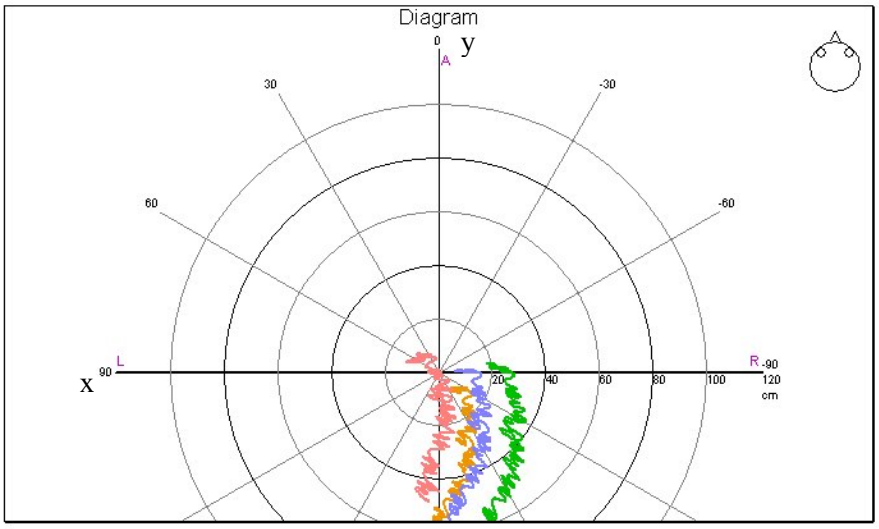

Figure 7. Representation of the sensor's registration on the PC monitor during Stepping test. (Figure taken from our clinical material).

This system uses different parameters, a total of four, for each of the vestibulospinal tests. The parameters for evaluating the standing test are the longitudinal sway and lateral sway in cm, the forehead covering area in cm^2, and the torticollis angle in degree. The parameters for the stepping test evaluation are the longitudinal deviation

and lateral sway width in cm, the angular deviation and self spin in degree [48] (Figure 8.).

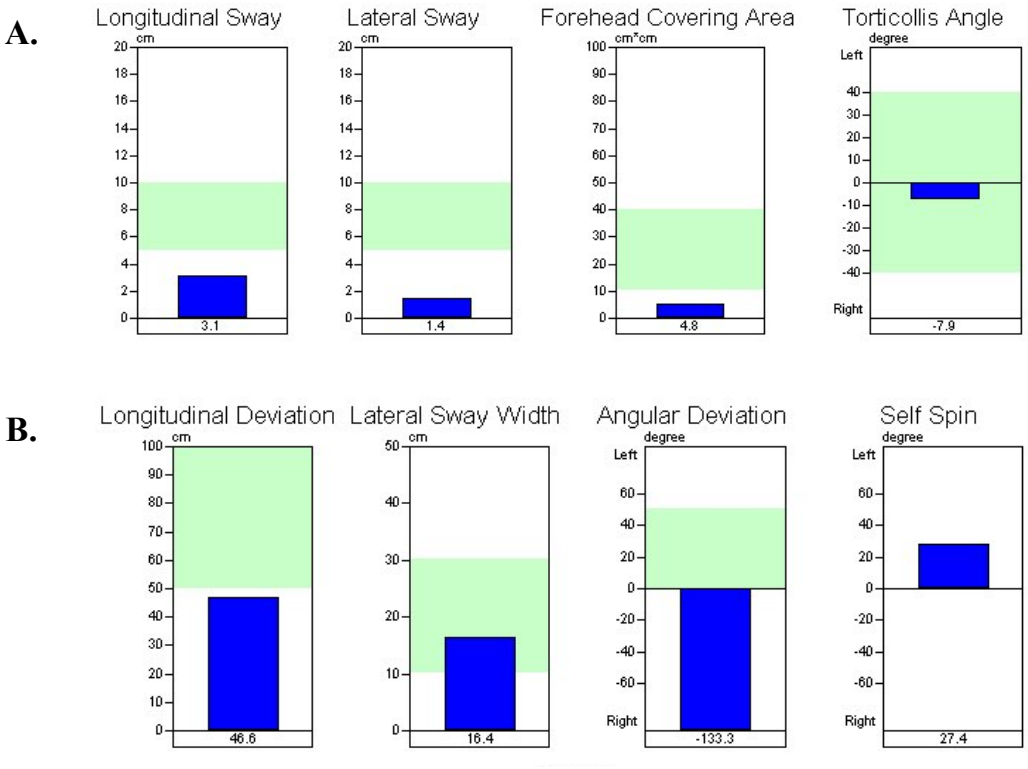

Figure 8. Parameters registration in **A.** Standing test and **B**. Stepping test based on US-COMP-CCG. (Figure taken from our clinical material).

1.2.1. Standing test (Romberg's test)

Standing test is an exam of VSR function for balance. The Romberg test was first described in 1846 [49]. The examination is based on the principle that a person requires at least two of the three following senses to maintain balance while standing: proprioception; intact vestibular function, and vision [50]. The Romberg test is used to investigate a stance disturbance resulted by abnormal proprioception, and therefore to diagnose sensory ataxia. It is also evidenced to be sensitive and accurate means of measuring the degree of disequilibrium resulted by central or peripheral vertigo and head trauma [51]. The patient is requested to stand still with their feet together, hands stretched down, and eyes closed for a period of approximately 1 minute (Figure 9.). This leaves out of the three compartments, only two and if there is a vestibular

dysfunction, labyrinthine or a proprioceptive dysfunction, sensory disorder then the patient will show much more unbalanced. A positive Romberg test suggests that the ataxia is in nature sensory, consequently depending on loss of the proprioception and the patients deviates towards the side of the lesion [52]. In the case of a patient is ataxic and the test is not positive, it suggests that ataxia is cerebellar, therefore depending on localized cerebellar dysfunction.

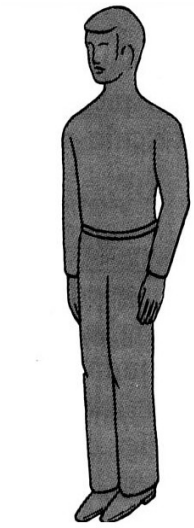

Figure 9. Illustration for Romberg' test performance by an individual. (https://www.intechopen.com/books/anxiety-and-related-disorders/anxiety-in-vestibular-disorders).

1.2.2. Stepping test (Unterberger-Fukuda's test)

Unterberger had described the tendency of vestibular stimulation to turn the patient in the vertical axis of earth when walking [53]. Fukuda in 1959 named this examination combined waltzing test by Hirsch (1940) as stepping test. It is suggested to indicate the weaker of the labyrinths, but not necessarily the side with the lesion, by the direction of the rotation of a patient while walking in place with eyes closed [54]. The test is carried out by asking the patient to stand with their arms extended, and to close their eyes during a period of 1 minute (Figure 10.). The patient is asked to march on the spot and the angle of rotation as well as forwards and backwards movements is

recorded. A rotation of 45° or greater is considered significant, suggesting a peripheral vestibular deficit towards the side of rotation [55]. However, in the rotation angle there is a pronounced variability based on one subject to another

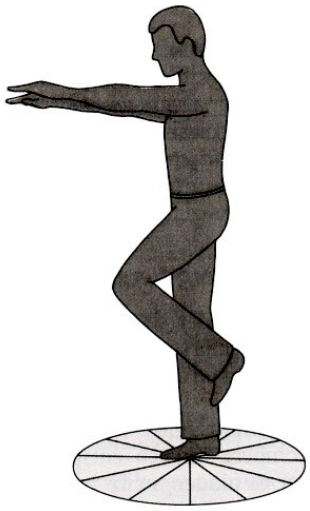

Figure 10. Illustration for Unterberger's - Fukuda test performance by an individual. (https://www.intechopen.com/books/anxiety-and-related-disorders/anxiety-in-vestibular-disorders).

1.3. Caloric vestibular test (CVT)

CVT is a neurootologic assessment tool for the function of the vestibuloocular reflex. Caloric testing is based on the principle of generating thermal variation within the external auditory canal [56] and as a result endolymph flow in the horizontal semicircular canals. The bithermal CVT is used to assess lateral semicircular canal function on both sides of the head separately, also with the function of superior parts of the vestibular nerve [57]. The test is done using a CHARTR air caloric stimulator, NCA-200. Air stimulus is used (with constant airflow at 25˚C and 50˚C, 5 litre/minute for 40 seconds), and eye movements are recorded by an electronystagmography system. After irrigation, the induced nystagmic response is characterized by its slow-phase velocity. A modified Jongkees' formula is used to define canal paresis (CP%) and directional preponderance (DP%) parameters for further statistical analysis [58]. The

CP% parameter is calculated as the difference of the maximum slow-phase velocity between the two labyrinths [59].

1.4. Peripheral Vestibular disorders (PVD)

Generalized symptoms of peripheral origin vertigo include a sudden, memorable onset with spontaneous, paroxysmal events lasting less than 24 hours in most cases. Where in few cases, head movements provoke the symptoms and are lasting from seconds to couple of minutes. Nystagmus is usually directional fixed, dominantly horizontal. Presence of abnormal VOR, with saccade performance is considered to be normal. These disorders include BPPV, vestibular neuritis, MD, labyrinthitis, vestibular migraine, and vestibulopathy following surgical procedures (e.g. labyrinthectomy) (Table 1.).

Table 1. Table of PVD according to frequency.

Peripheral Vestibular disorders	Vertigo attacks length	Acute hearing loss/tinnitus?	Headache
1.BPPV	Seconds, minutes	No	No
2.Vestibular neuritis	Days	No	No
3.Ménière's disease	Hours	Yes	Probable*
4.Labyrinthitis	Days	Yes	No
5.Vestibular migraine	Varies	No	Yes

* in 49% cases, headache was indicated as MD complain (Radtke A, Lempert T, Gresty MA, Brookes GB, Bronstein AM, Neuhauser H. (2002) Migraine and Ménière's disease: is there a link? Neurology, 59: 1700-1704).

1.4.1. Ménière's disease (MD) and Ménière-syndrome

The physician Prosper Ménière in 1861 theorized that episodic attacks of vertigo, tinnitus and hearing loss came from the inner ear rather than from brain parts.

Once this suggestion was accepted, physicians name began its long association with this particular inner ear disease and with inner ear balance disorders in general. The disease was later described in 1938 by Hallpike and Cairns, which indicated the principal underlying pathology, the endolymphatic hydrops, and therefore the consequences upon the system [60, 61]. In 1995 the Committee of Hearing and Equilibrium of the American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) defined it as “the idiopathic syndrome of endolymphatic hydrops” [62].

In the daily practice, there is often a mention to Ménière-syndrome, which differs from MD. In the case of Ménière-syndrome not many facts are known, compared to the vast knowledge about MD. It is known that the syndrome consists of a rotatory type of episodic vertigo spells, accompanied by vegetative symptoms which are not attributed to the endolymphatic hydrops, but is rather connected to other inner ear diseases (i.e. Lyme disease, syphilitic neurolabyrinthitis, perilymph-fistula, trauma, vascular etiologies). Nevertheless, in the background of the Ménière-syndrome, we cannot exclude the MD which is not that often [63].

MD cardinal symptoms include episodic vertigo, tinnitus and fluctuant hearing loss. These symptoms may be accompanied with fullness of the ear, gait problems, postural instability, nausea.

1.4.1.1. Epidemiology

Dizziness and vertigo are considered to be among the most common symptoms leading patients to visit their physician [64]. MD is considered to be the second most frequent vertigo disorder, predisposed by BPPV. It is much more common in adulthood, with an average age of onset in the fourth decade, the symptoms though may begin between ages 20 and 60 years. MD is equally common in each sex, and right and left ears are affected with fairly equal frequency [65, 66]. Based on studies made, the prevalence among countries vary, 200 cases/100,000 in the USA [67] to prevalences as low as fewer than 20/100,000 in Japan [68], and a level of about 46/100,000 in Scandinavia [69, 70].

1.4.1.2. Ménière's disease pathophysiology and causes

MD is considered to be a disorder of the membranous labyrinth, with variety of cochlear and vestibular symptoms; manifesting themselves as vertigo, sensorineural hearing loss, tinnitus, aural fullness and vegetative symptoms, such as nausea and vomiting. The pathophysiologic entity, and the hypothesis of MD, is based on the endolymphatic hydrops [71]. With increase of the endolymphatic hydrops, there is a potential risk of a rupture in the membranous labyrinth, with the sequential mixing of endolymph and perilymph and therefore, the changing levels of potassium are presumed to give rise to the vestibular symptoms. The rupture of the membrane due to hydrops is thought to explain the amelioration of the cochlear symptoms when vertigo appears. Moreover, the repetition of hydrops crises and repeated rupture of the membrane are considered, to bring upon a progressive destruction of the labyrinth and eventually resulting to the evolution of profound deafness and disappearance of vertigo [72]. Also, the roles of internal medicine disease should be emphasized in the MD. Such diseases include diabetes and hypertension [73], which may be an indicator for an upcoming MD attack.

1.4.1.3. Clinical features of Ménière's disease

MD is defined by the classic triad of vestibular and cochlear symptoms, aural pressure and vegetative symptoms. Duration of the episodes varies in a range of 20 min up to 24 hours and these episodes are reoccurring in the following months [74]. Even though vertigo symptoms may decline due to a "burn-out" of the inner ear, studies have shown a progression of the intensity of the vertigo symptoms during the long course of MD [63].

Hearing loss is described as sensorineural, where at first, it is resolved completely between attacks, and in the early stages, low frequency (200 - 600 Hz) hearing loss can be detected with fluctuating tendency using pure tone audiometry (PTA) [75]. In later stages, a progressive deterioration of hearing loss across the whole frequency spectrum is detected [76].

1.4.1.4. Staging of Ménière disease

MD may be divided in three stages according to the attacks rate and the complaints of the patient in the attack-free period [77].

Stage I (early): occurs in the early phase, where the predominant symptom is vertigo. The vertigo attacks are rare and are of rotatory nature. Nausea or vomiting may be present. The episode may be preceded by an aura of fullness in the affected ear and usually lasts from 20 minutes to several hours. During the attack-free period hearing reverts to normal and the balance is intact.

Stage II (intermediate): the disease advances, the severity of vertigo increases, as well as its frequency. The hearing loss become established and more severe, but it continues to fluctuate. Characteristically, the progressive sensorineural hearing loss is found in the lower frequencies. Balance problem is more profound, the period of remission is highly variable, often lasting for several months.

Stage III (late): is the last, most severe stage. The episodes of vertigo may diminish, there is permanent damage to the balance organ and significant general balance problems are common, especially in the dark. There is no more fluctuation in the hearing loss and progressively worsens. The hearing levels remain down below 60 dB. All of these, eventually and consequently result in a poor QoL [61, 78].

1.4.1.5. Therapeutic management of Ménière's disease

Acute treatment

In the acute phase the first goal is to control and/or stop the rotatory vertigo attacks as well as the accompanying nausea and vegetative symptoms that might be existing. Conservative drug treatment with anti-emetics, vestibulo-sedative antihistamines (e.g. betahistine) [79], and central sedative drugs with vestibulo-suppressive or anti-emetic effect can be useful.

Long-term treatment

The goal here is to prevent or diminish further attacks of vertigo, to provide assistance for the compensation for the vestibular deficit, to assist with the hearing loss

and associated symptoms. Modalities suggested here include lifestyle and eating habits adaptation (salt restriction and avoidance of caffeine, alcohol, tobacco, and coping with stress), frequent consultations, drug therapy, rehabilitation, and a further non-conservative suggestion is surgery (according to the stage and progression of the illness).

Chronic drug therapy

Choices here include drugs that will not interfere with the vestibular compensation. Betahistine is one of the most frequent suggestions [80]. Diuretics may also be of benefit as it is described in some studies, although the use of acetazolamide in MD is still controversial [81, 82].

Mild vestibular sedatives such as cinnarizine may be of help, when the transition from acute to chronic treatment fails to alleviate symptoms. Concomitant diseases, like hypertension, and diabetes mellitus may influence the success of the treatment [66]. Therefore, to achieve a complete control over the attacks becomes more difficult.

Intratympanic (IT) administration of drugs

IT application of steroids and ototoxic agents, based on the severity of the complaints, have been found to have a positive effect [83]. Itoh and Sakata first reported the protocol for an IT injection in 1987 [84]. Steroid administration (eg. dexamethasone) locally is considered one of the first-line treatments of acute sensorineural hearing loss, as well of the hearing loss in MD [84, 85]. The administration of aminoglycoside antibiotics (gentamicin) is considered a local destructive medical treatment and is known as agents for chemical vestibular ablation [86] (chemical labyrinthectomy). The prior mentioned procedure was first used by Schuknecht in 1957 [87].

The passage of the IT administrated drugs into the inner ear are across the tympanic membrane and by diffusion method from the middle ear into the inner ear through the round window [82]. Two main potential advantages: reaching higher concentration in the perilymph with lower doses and therefore, the systemic adverse

effects could be avoidable [88]. Possible non-frequent complications of IT use include post-IT injection vertigo, tinnitus, burning sensation, small perforation, and pain [89]. In the case of gentamicin administration, a complete or incomplete ablation of vestibular function is expected, whereas the differences in the therapy outcome are based on individuality of peripheral vestibular function and central compensation [90].

Psychological aspect

For the psychological handicap aspect of MD, anti-depressive treatment (i.e, selective serotonin reuptake inhibitors) may help in a pre-existing depression, but is not beneficial to vertigo itself neither in patients without pre-existing depression [91].

Surgical therapy

When the conservative therapy has failed, the surgical treatment may be of an advance. In failed cases of therapy the vertigo may become incapacitating. Less invasive treatment option may be the ventilation tube insertion, which may have positive short-term effect on the reduction of persistent vertigo [92]. The surgical options include labyrinthectomy, vestibular neurectomy, endolymphatic sac surgery and stapedius and tensor tympani muscles tenotomy [93, 94].

1.4.2. Benign Paroxysmal Positional Vertigo (BPPV)

BPPV is a disorder of the inner ear characterized by repeated brief episodes of rotating vertigo [95], triggered by changes in head and body position, without tinnitus or/and hearing loss. Is one of the most common and treatable causes of peripheral vestibular vertigo, with a higher incidence in elderly people [96], and prevalence is estimated to 2.4% in the general population [97]. Exact etiology is still not clear, in the most cases is idiopathic in nature; other cases are secondary. Commonly recognized conditions associated with secondary BPPV are vestibular neuritis, MD, head trauma, and postsurgical, as well as sudden sensorineural hearing loss and migraine can be implicated in the pathogenesis of secondary BPPV [98]. The clinical presentation is assumed to be caused by free-floating particles leaving the macula of the utricle and

entering one of the semicircular canals, usually the posterior and less frequently the lateral or anterior ones. Other secondary potential causes include diabetes mellitus, osteoporosis, inner ear disease including infection [99]. Alterations relating to this presentation, are related to the vestibular system, which therefore may cause multiple neurotological-associated symptoms, which include changes in body balance, gait disturbance, and occasional falls [100].

1.5. Central Vestibular disorders (CVD)

Any injury to the central vestibular system, as well as to the peripheral vestibular system, causes an asymmetry in the baseline input. This is resulting in vertigo, nystagmus, and instability [101]. Vertigo in this case results from either disruption of central integrators, sensory information mismatch, or affection of the primary vestibular sensory input. Typical CVD is evoked by dysfunction within the temporoparietal cortex, thalamus, brainstem and cerebellum, whereas it can be classified by characteristic perceptual and ocular motor manifestations, in addition to sensorimotor control of posture and gait [102].

CVD include brainstem strokes, head trauma, migraine-related vestibulopathy, multiple sclerosis, and cerebellar degeneration [103]. The younger population is more commonly affected by migraine associated vertigo and multiple sclerosis. On the other hand, older population is typically affected due to the associated risk factors of vascular causes of vertigo that include one or more of the following: hypertension, atherosclerosis, and diabetes mellitus [104].

Characteristics upon the dizziness include sudden onset of vertigo, imbalance with one of the “D's" (diplopia, dysarthria, dysmetria, dysdiadochokinesia). Nystagmus is more likely to be enhanced with fixation present, whereas might be torsional and post-head shake vertical. Saccades are likely to have abnormal performance, as well as on pursuit.

1.6. Gait disorders

Postural symptoms are balance symptoms related to maintenance of postural stability, occurring only with an upright position with or without motion involved. Unsteadiness, on the other hand, is the sensation of being unstable while standing, or walking without a particular directional preference [105]. In order to maintain a normal gait all of the following functions and systems must meet and be intact: locomotor function - rhythmic gait initiation and sustainability, balance, postural reflex, sensory function and sensorimotor integration, motor control, the muskuloskeletal apparatus and cardiopulmonary functions. From the visual, vestibular and proprioceptive systems afferent nerves provide necessarily information on position of the body and its parts [106]. Any disturbances among these mentioned systems, may be partially compensated by other sensory system. A centrally integrating system, involving areas in the frontal cortex, the basal ganglia, the brain stem and the cerebellum, analyzes the information received and selects the motor programs required for walking. On the other hand, the efferent system comprises descending pathways including the pyramidal tract, peripheral nerves, neuromuscular end plate and muscles. The brain stem centers, in particular the midbrain locomotor center, which is including the pedunculopontine nucleus, have a central role in generating automatic walking [106].

A stable upright body position is required for initiating gait and functioning postural reflexes are of necessity to maintain a stable position. The gait cycle contains two phases, e.g., stance and swing phase, of which stance phase constitutes for approximately 60% of the cycle and swing phase the remaining percentage [107].

1.7. HINTS (+)

Commonly used bedside test in the evaluation of acute vertigo episodes includes the HINTS (or HINTS+) exam [108]. Three components are included in the HINTS testing: head impulse, nystagmus, and test of skew.

Head impulse test assesses the VOR and a corrective saccade is generated in the case of peripheral weakness. Benign peripheral vestibular lesions usually are characterized by unidirectional horizontal nystagmus and increases with fixation block

[109]. However, in central lesions, this nystagmus pattern may be found and therefore is not a localization finding. On the other hand, the horizontal gaze direction changing nystagmus is a specific sign of a central lesion, as well as the presence of vertical and/or purely torsional nystagmus is the result of it as well [110]. Skew test is considered as s sign of an abnormal otolith-ocular reflex; thus large amplitude skew deviation and the ocular tilt reaction are more common findings with central lesions [111].

The HINTS(+) test includes the additional assessment for acute unilateral hearing loss. Hearing loss due to cochlear or brainstem ischaemia can potentially increase diagnostic accuracy. The vascular supply to the inner ear, is most frequently from anterior inferior cerebellar artery, the basilar artery and only rarely via posterior inferior cerebellar artery [112].

In patients with at least one risk factor for stroke, HINTS(+) have a higher sensitivity and specificity for detecting a central cause of vertigo [113]. This bedside exam was developed in order of assessing patients with the acute vestibular syndrome (AVS) [114]. The AVS is defined as the acute onset of vertigo lasting longer than 24 hours, associated with gait instability, nausea, vomiting and head motion intolerance [114]. Patients suffering of acute vertigo episodes will visit the ED and seek further help. Therefore performing the HINTS(+) exam is of importance and if any portion of the test is in keeping with a central etiology of vertigo, acute treatment is needed. Central and peripheral interpretation of the test is shown in the Table 2 [115].

Table 2. Interpretation of the HINTS(+) exam in acute complaints [115].

HINTS (+) exam component	**Vestibular neuritis (peripheral)**	**Pseudoneuritis (central)**
Head Impulse Test	Loss of eye fixation: positive	Intact VOR: negative
Nystagmus	None or horizontal unidirectional	Vertical, rotatory, or horizontal bidirectional
Test of skew	No skew: negative	Skew presence: positive
Acute hearing loss	No	Yes

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2. Objectives

The efficacy of bedside diagnosis in our ED, and the acute vertigo episode correlation with the ED diagnosis, as well as the QoL were the first objectives of the research.

The study of balance system and moreover the US-COMP-CCG investigation method capabilities was the next objective of the research, from a simple diagnosis of vestibular disorders to the complete follow-up of a treatment regimen registration possibility.

Last objective of the research was to evaluate the relationship between the cochlear and vestibular function loss in MD, by the means of PTA and CVT.

2.1. Acute vertigo episode in the Emergency department

2.1.1. Emergency department diagnosis of the vertiginous population

A questionnaire was distributed to the patients who visited the ED with acute vertigo complaints. Aim was to investigate the efficacy of bedside examination based on the documentations, and to follow-up the population. More precisely, the given diagnosis and the direction they were referred to it for further help in their complaints. Important aim was to examine whether the patients suffering from typical peripheral vestibular lesions were sent to neurotological or at least otorhinolaryngological examination or not.

2.1.2. Assessment of the patients' quality of life visiting the Emergency department with dizziness

Along with the questionnaire, the Dizziness Handicap Inventory (DHI) was attached. Aim was to investigate the effects of even a single acute vertigo attack in the population. Consequently, register the QoL of the vertiginous population.

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2.2. US-COMP-CCG abilities

2.2.1. Different stages in Ménière's disease based on US-COMP-CCG

MD clinically is a progressive disease and can be classified into 3 different stages, based on the vertigo attacks and the symptoms in the attack-free period. Aim of the study was to see if the objective registration of these stages is possible, and how the clinical progression correlates with the worsening of US-COMP-CCG parameters.

2.2.2. Intratympanic steroid therapy for advanced MD in correlation with the vestibular system

In the investigation of ITS injection (dexamethasone) effects, most studies are based on the vertigo spell and the hearing loss improvement. Aim in our study was to investigate the effects of the treatment on the vestibular system in patients suffering from an advanced MD.

2.2.3. Differentiation between idiopathic and secondary BPPV based on the US-COMP-CCG results

BPPV is one of the most common backgrounds of vertigo, and the etiology can be classified into idiopathic (i-BPPV) or secondary (s-BPPV). To distinguish between these etiologies the US-COMP-CCG was used. Our hypothesis was that the i-BPPV does not affect the VSR, while the s-BPPV has influence on the US-COMP-CCG parameters.

2.2.4. The diagnosis of central vestibular disorder based on the complementary examination of the vestibulospinal reflex

The aim of the study was to characterize the gait unsteadiness in patients suffering from central vestibular disorder and discuss the possible diagnostic usage of US-COMP-CCG, and therefore the objective estimation of postural imbalance.

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2.3. Comparative study between the auditory and vestibular functions in Ménière's disease

In MD the cochlear and the vestibular functions are affected. The purpose of the investigation was to study retrospectively the topodiagnostic relationship between the cochlear and vestibular function loss in MD, using CVT and PTA.

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3. Methods

3.1. Acute vertigo episode in the Emergency department

The study was set in a single medical centre (Emergency department of Semmelweis University) data. The study had permission from the Semmelweis University Regional and Institutional Committee of Science and Research Ethics 28/2018.

We analyzed data of the last 2.5 years (2017, 2018 to first six months of 2019) from ongoing, institutional board-approved, diagnostic study of vertiginous population seeking first treatment for dizziness or vertigo. Inclusion criteria were based on the diagnosis given in the ED documentation. Number of patients included was 879. Out of the 879 patients, 308 (110 males and 198 females, mean age ± SD, 61.8 years ± 12.3) have answered the questionnaire, which were further analyzed [116]. The proportion of female patients among non-responders was 64%, mean age ± SD, 58.7 years ± 4.31, and based on statistical analysis there was no significant difference ($p = 0.15$) compared to the age of the respondents, which means that the examined sample can be considered representative for the population. The distribution of diagnosis among non-responders was as follows: dizziness (24.71%), central dizziness (28.12%), BPPV (19.64%), other peripheral causes (12.05%), vestibular neuritis (5.89%), vestibular migraine (1.49%) and MD (2.55%).

Based on the diagnosis given in ED, we distributed a questionnaire with different symptoms related to the vestibular system, as well as the DHI attached to it in the Hungarian language.

In the first part of the questionnaire, we asked and compared the various complaints that accompanied the vertigo/dizziness, the diagnosis made to the ED and the subsequent diagnosis (which may include only a visit to the General Practitioner - GP). The first part of the questionnaire is presented in Figure 10.

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The following questions relate to what happened to you after you left the emergency room

Did you visit your GP?	Yes	No
Did you visit an ENT specialist?	Yes	No
Did you visit a Neurology specialist?	Yes	No
Did you visit an Internal medicine specialist?	Yes	No
Did you consult another specialist?	Yes, namely: ……	No
Have you been sent to neurotology examination?	Yes	No

Please briefly write in your own words what your doctor found after the examinations were completed:

……

……

……

Please, underline the most typical response, indicating how much time has elapsed before you received a final diagnosis:

Days Weeks Months One year

No final diagnosis was given I do not know

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Acute dizziness patients follow-up questionnaire

Was it a spinning type of vertigo?	Yes	No	I do not remember
How long did it last?		seconds, minutes, hours, a day, many days, since then, I do not remember	
Nausea?	Yes	No	I do not remember
Vomiting?	Yes	No	I do not remember
Hearing loss?	Yes	No	I do not remember
Buzzing of the ear?	Yes	No	I do not remember
Vision complaints?	Yes	No	I do not remember
Syncope?	Yes	No	I do not remember
Headache?	Yes	No	I do not remember

When you were released from the emergency room, what was told to you what caused the dizziness?

……

……

Figure 11. First part of the questionnaire presented to the patients who visited ED with acute vertigo complaints [115].

Second part of the questionnaire included the DHI. The DHI questionnaire is a widely use questionnaire for the evaluation of the self-reported disability in patients suffering from dizziness and balance problems, and overall can provide a self-perceived

QoL measurement (Figure 12.). The items which are included in the DHI were originally derived from case histories of patients with dizziness, and for the scoring scale several studies were performed involving patients seen for vestibulometric testings.

The DHI contains an overall of 25 items, and a total score (0 - 100 points) is obtained by summing ordinal scale responses, whereas higher scores indicate a more severe handicap. The scale was developed to capture various subdomains of self-perceived handicap and it comprises 7 physical (P), 9 functional (F), and 9 emotional (E) questions (Figure 14.). Score interpretation is as follows: yes: 4 points, sometimes: 2 points and no: 0 point is given. Consequently, the handicap scores are the following: 16 - 34 points is considered mild handicap, 36 - 52 points is a moderate handicap, whereas 54+ points is of a severe handicap [115, 116].

1.	Does looking up increase your problem?	Yes	Sometimes	No
2.	Because of your problem, do you feel frustrated?	Yes	Sometimes	No
3.	Because of your problem, do you restrict your travel for business or recreation?	Yes	Sometimes	No
4.	Does walking down the aisle of a supermarket increase your problem?	Yes	Sometimes	No
5.	Because of your problem, do you have difficulty getting into or out of bed?	Yes	Sometimes	No
6.	Does your problem significantly restrict your participation in social activities, such as going out to dinner, going to movies, dancing, or to parties?	Yes	Sometimes	No
7.	Because of your problem, do you have difficulty reading?	Yes	Sometimes	No
8.	Does performing more ambitious activities like sports, dancing, household chores such as sweeping or putting dishes away increase your problem?	Yes	Sometimes	No
9.	Because of your problem, are you afraid to leave home without having someone with you?	Yes	Sometimes	No
10.	Because of your problem, have you been embarrassed in front of others?	Yes	Sometimes	No
11.	Do quick movements of your head increase your problem?	Yes	Sometimes	No
12.	Because of your problem, do you avoid heights?	Yes	Sometimes	No
13.	Does turning over in bed increase your problem?	Yes	Sometimes	No
14.	Because of your problem, is it difficult for you to do strenuous housework or yardwork?	Yes	Sometimes	No
15.	Because of your problem, are you afraid people may think you are intoxicated?	Yes	Sometimes	No
16.	Because of your problem, is it difficult for you to go for a walk by yourself?	Yes	Sometimes	No
17.	Does walking down a sidewalk increase your problem?	Yes	Sometimes	No
18.	Because of your problem, is it difficult for you to concentrate?	Yes	Sometimes	No
19.	Because of your problem is it difficult for you to go for a walk around your house in the dark?	Yes	Sometimes	No
20.	Because of your problem, are you afraid to stay home alone?	Yes	Sometimes	No
21.	Because of your problem, do you feel handicapped?	Yes	Sometimes	No
22.	Has your problem placed stress on your relationship with members of your family or friends?	Yes	Sometimes	No
23.	Because of your problem, are you depressed?	Yes	Sometimes	No
24.	Does your problem interfere with your job or household responsibilities?	Yes	Sometimes	No
25.	Does bending over increase your problem?	Yes	Sometimes	No

Figure 12. The DHI questionnaire [116].

3.2. US-COMP-CCG abilities

US-COMP-CCG is based on a mathematical analysis and the principle is installed into the ZEBRIS Coordinate Measurement System® (Isny, Germany). To objectively measure the balance and postural stability in patients with vestibular disorders the standing and stepping test of US-COMP-CCG was used. After the computer calculated the parameters, the results of the control patients and of those involved in the different disorders were contrasted. To diagnose the vestibular disorders, complete neurotological examination was used, including anamnestic data, otoscopy, electronystagmography (ENG), video-head impulse test (vHIT), and complementary examinations if it was necessary (e.g. magnetic resonance imaging (MRI), carotid vertebral Doppler ultrasound, PTA). The main parameters, which were recommended by the manufacture, to evaluate the standing test and the stepping test for statistical analysis is presented in the Table 3.

Table 3. Suggested parameter values for analytical and statistical usage. (Table taken from our clinical material).

Standing parameters				
	Longitudinal sway (cm): › 10	Lateral sway (cm): › 10	Forehead covering area (cm^2): › 50	Torticollis angle (degree): › 0
Stepping parameters				
	Longitudinal deviation (cm): › 10	Lateral sway width (cm): › 10	Angular deviation (degree): › 45	Self spin (degree): › 45

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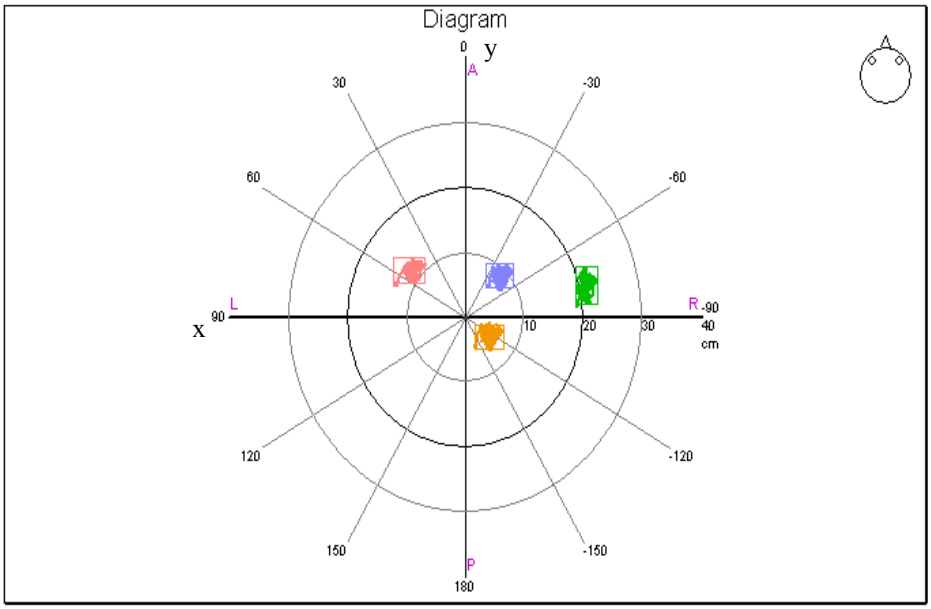
The presentation of the vestibular disorders through the registration of the US-COMP-CCG are represented differently schematically and analytically. The displacement in the anterior, posterior and right (-), left (+) directions within the base of support appears in as the radar images of four moving objects, progressing in an interrelated direction, in one or several polar planes. Anterior marker is blue, posterior marker is orange, left localized shoulder marker is red and right shoulder marker is green. By assessing the US-COMP-CCG picture as a whole, the difference between healthy subjects and patients with vestibular disorder usually is seen as qualitative. That is, the subjects' and patients' movement patterns could be differentiated at first glance on the craniocorpogram.

The format of the graph is using numerical coordinates across perpendicular lines (x,y). If the marks are moving on the X axis, that means a longitudinal deviation (lateral sway), which is more typical for peripheral lesions. If they are moving on Y axis, that is a vertical deviation (sagittal sway), which could be detected in case of central dysfunction. A unilateral peripheral lesion registration is shown in the Figure 13. A wide angular deviation, i.e., where the patient deflects more than circa 45 degrees away from the sagittal axis, is taken to signify a peripheral dysfunction, usually involving the side of deviation.

A.



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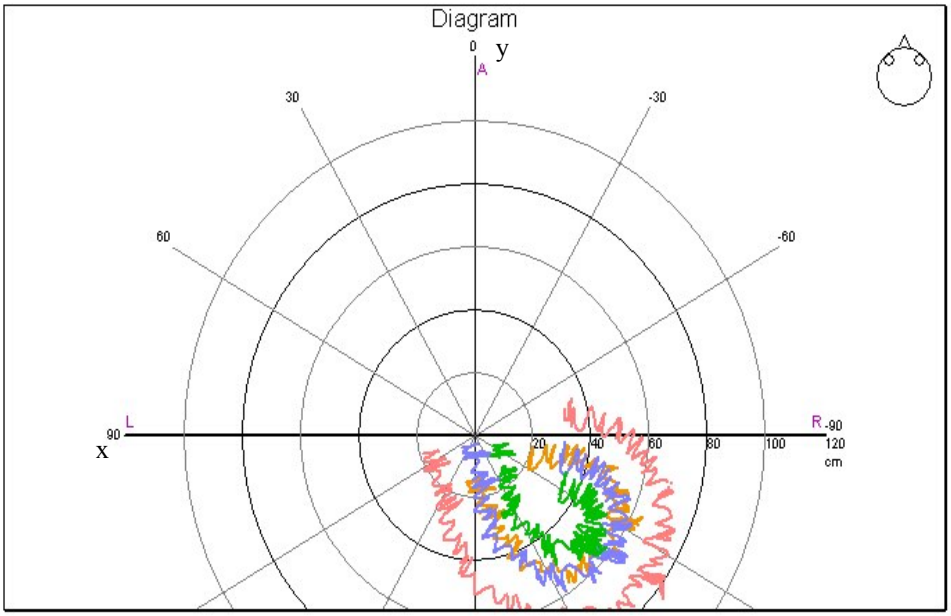
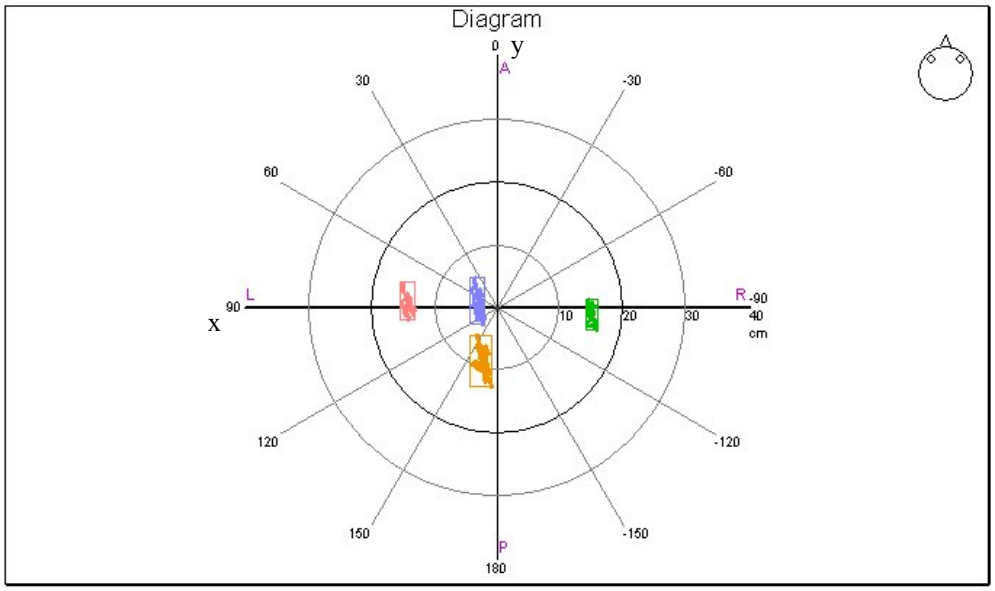


Figure 13. Unilateral peripheral lesion representation in **A.** Standing test, and **B.** Stepping test. In the standing test parameters are moving on the X axis; in the stepping test deviation over 45 degrees is detected [44].

Lesion representing a central vestibular cause on the US-COMP-CCG is shown in the Figure 14. Broad lateral sway values and standing tests sways suggest a central pathology. As well in stepping test we can detect the postural ataxia of the patient.



B.

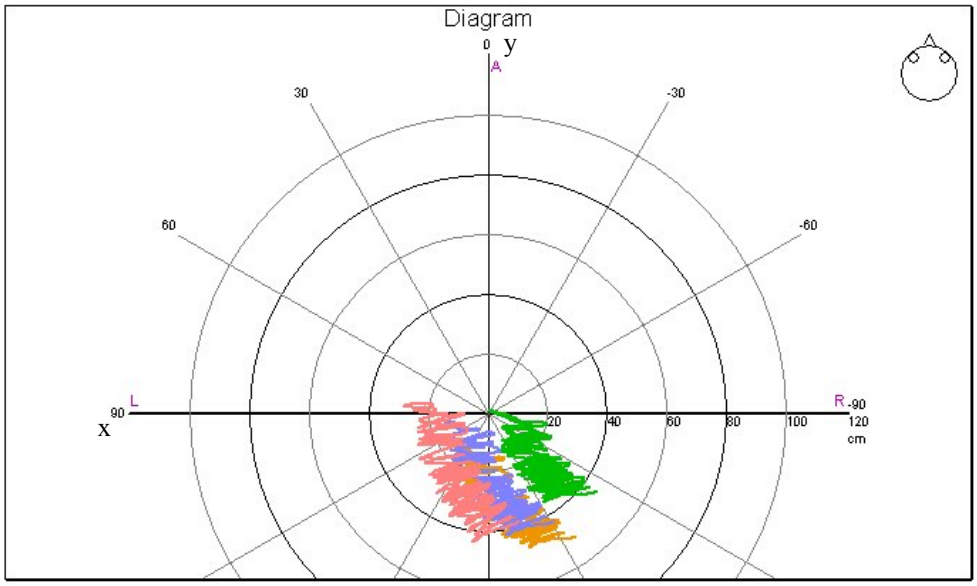


Figure 14. Central vestibular lesion representation in **A.** Standing test, and **B.** Stepping test. In the standing test the parameters are moving on the Y axis, and in the stepping test the stop of the walking during the test was detected. (Figure taken from our clinical material).

Control patients were referred to neurotology in all study groups because of sensorineural hearing loss or tinnitus without vertigo and balance disorder symptoms.

All of the studies under the section were performed at the Neurotological department of Semmelweis University. Conducting the study was permitted by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics 190/2015.

In the MD staging research 42 patients with definite MD participated and 51 patients were included in the control group. Patients were included with age 24 -76 years, so the age interval for the control subjects was the same (mean age ± SD, 56.3 years ± 10.2 of MD patients, 55.6 years ± 9.4 of control patients). In both groups, the distribution by gender was: 76% females, 24% males [118]. Based on AAO-HNS criteria the patients were selected. This criteria states that the diagnosis of definite MD

is based on the clinical criteria and requires the observation of an episodic vertigo associated with low- to medium-frequency sensorineural hearing loss and fluctuating aural symptoms (tinnitus and/or fullness) in the affected ear. Duration of vertigo episodes fluctuate to a period between 20 minutes and 12 hours. A broader concept is the probable MD, defined by episodic vertigo or dizziness associated with fluctuating aural symptoms occurring in a period from 20 minutes to 24 hours [64]. Patients with probable MD, motion sickness, and vestibular migraine were excluded from the study. Bilateral MD with or without autoimmune disease were also excluded [117].

Thirty-eight patients suffering from advanced MD (13 male and 25 female patients, mean age ± SD, 56.3 years ± 10.2) who received ITS therapy and 82 patients (37 male and 45 female patients, mean age ± SD, 60.8 years ± 10.6) with advanced MD who had not received ITS were enrolled in this investigation and examined using US-COMP-CCG. All patients participating in our study fulfilled the diagnostic criteria for MD according to the recommendation of the Bárány society. Patients with probable MD, motion sickness, and vestibular migraine were excluded from the study. Bilateral MD with or without autoimmune disease was also excluded. Patient selection was made based on the clinical staging criteria of MD (stage I: rare attacks, II: severe and recurring attacks, III: severe constant hearing loss, disabling balance problems, severe attacks) and based on the objective staging measurements of US-COMP-CCG. More specifically, patients suffering from stage III were selected and therefore, the administration of ITS (dexamethasone) injection was decided. By this means the gait system could be measured before and after administration. As per the hospital protocol, the test was firstly performed before the first ITS administrated treatment and re-measured two weeks after the last treatment. Determination for an abnormal postural control was based on the standing and stepping test parameters of US-COMP-CCG. Categorisation for abnormal was based on changes in any two out of four parameters for each test [118].

In the BPPV research 135 patients with age between 15 - 80 years, 31 males and 101 females with symptoms of BPPV (mean age ± SD, 56.8 years ± 12.2) and a control group consisting of 140, 43 male and 97 female patients (mean age ± SD, 50.8 years ± 15) were enrolled. Patients with imbalance, suffering from i-BPPV and s-BPPV were included and exclusion criteria were patients with systemic illness. 109 patients suffered from i-BPPV, and 26 patients from s-BPPV [44].

The CVD analysis was a prospective study, whereas 420 patients were selected in the period of 2 years who were referred with complaints in our tertiary referral neurotological department. Inclusion criteria were based on the previous documented neurology findings and the neurotology examinations, including ENG with bithermal caloric test, vHIT, brain imaging and US-COMP-CCG, as well as complementary examinations were carried out (PTA, BERA - brainstem evoked response audiometry). Central vestibular lesions in the neurotology praxis were defined by bithermal caloric test with ENG registration which were indicated according to ipsilaterally caloric reduction. vHIT showed no abnormality in these cases but helped in the definitive discrimination between peripheral and central vertigo. Exclusion criteria for the selection of the participants were medications that could influence the vestibular system, physical limitation, and influence of alcohol and/or drugs, as well as patients diagnosed with peripheral disorders. According to the results of the former examinations, 190 patients (70 male and 120 females, mean age SD, 58.94 ± 15.27) suffering from a central vestibular disorder were enrolled. Based on the medical documentation, 17% had vascular encephalopathy, 4% multiple sclerosis, 25% vertebrobasilar insufficiency, 37% generalized ischaemia, 1% probable migraine vestibulopathy, 3% acoustic schwannoma. 230 subjects (78 male and 152 females, mean age SD, 50.94 ± 15.27) with no vestibular complaints, who were referred to neurotology because of hearing loss and/or tinnitus were also investigated. Vertigo or instability was absent, and the complete neurotological examination as well as the complementary examinations did not show any pathologic aberration.

3.3. Comparative study between the auditory and vestibular functions in Ménière's disease

Forty-three patients (18 males and 25 females, mean age ± SD, 54.8 ± 13.3) admitted to the tertiary care referral center of Department of Otolaryngology and Head Neck Surgery, Semmelweis University, who were diagnosed with definitive MD according to the Bárány Society criteria, were analyzed retrospectively, from the onset of MD to the neurological examination. All participants were evaluated using both CVT and PTA. Patients with incomplete medical history, bilateral MD, who were treated with IT treatment and patients suffering from other peripheral vestibular disorders were excluded. To exclude vestibular schwannoma MRI was used. Conducting the study was permitted by the Regional and Institutional Committee of Science and Research Ethics at Semmelweis University: 48/2018 [119].

Audiometric examination was performed using PTA. Extended Fletcher Index was used to calculate hearing loss. Extended Fletcher Index is the average hearing loss detected on 500, 1000, 2000 and 4000 Hz frequencies [120]. Based on the AAO-HNS classification the staging according to the PTA stages is as follows: stage A: ≤ 25 dB, stage B: 26 - 40 dB, stage C: 41-70 dB, and stage D: > 70 dB. To rule out the effects of ageing (i.e. presbycusis) on hearing, the interaural difference of the hearing level (dPTA) was also calculated defined as the difference between the healthy and diseased PTA stages.

Both tests (PTA and CVT) were performed during the same control to rule out the fluctuation characteristic of the disorder. None of the patients were in acute episode of MD during the examinations [119].

3.4. Statistical analysis

The statistical analysis was performed using IBM SPSS V24 software. As most of the studied parameters did not show normal distribution (Shapiro-Wilk test), non-parametric test were used (Mann-Whitney U test). For categorical analysis Fisher-exact test, Chi-square test and Kappa-test were applied. To detect possible correlation between the parameters Pearson and Spearman rank correlations were applied. To determine

sensitivity (TPR - true positive rate) and specificity (TNR - true negative rate) parameters, receiver operating characteristic curves (ROC) were drawn, and the parameters were calculated based on area under curve (AUC). To investigate the long-term effects of applied therapy on balance, Kaplan-Meier curves were included, and logistic regression was used as well. The significance level was defined as $p < 0.05$ in all of the cases.

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4. Results

4.1. Emergency department diagnosis of the vertiginous population

The correlation between our ED diagnosis and final diagnosis given to the patient was the basis of the first study. Clarification of the final post examination diagnosis duration, and the follow-up was among the questions [115].

Based on the ED diagnosis documentation the following results were made as shown in Table 4.

Table 4. The ED distributed diagnosis [115].

Diseases	Number of patients
No specific diagnosis was given	74 (24.02%)
CVD	71 (23.05%)
Dizziness	64 (20.78%)
BPPV	51 (16.56%)
Other PVD	32 (10.32%)
Vestibular neuritis	10 (3.25%)
MD	4 (1.30%)
Migraine	2 (0.65%)

According to the results of the Table 4., among the PVD most usual diagnosis was BPPV (16.56%), followed by CVD (23.05%) and dizziness (20.78%).

It should be noted that in 24.02% of cases no specific diagnosis was made, which does not mean that no relevant diagnosis was made, but that the patient was not thoroughly informed of the possible cause of his/hers illness. Serious life-threatening illnesses were screened in the majority of cases, with 14.83% of patients having a confirmed transient ischemic attack (TIA)/acute stroke and a diagnostic failure rate of

9%, consistent with those reported in the international literature [120]. In their case, the efficiency of acute treatment was 37%. We sought to compare the results of these diagnosis and subsequent specialist examinations, and therefore we asked in the questionnaire what special examinations had been made after leaving the ED (Table 5.).

The follow-up of this vertiginous population was mostly done with their GP, and later consultation in neurology, ear-nose-throat (ENT), as well as internal medicine, was made for further help.

Table 5. After the emission from the ED follow-up of the patients, based on the areas they were referred to (based on patients answer) [115].

Specilization area	Number of patients
General practitioner	128
Neurology	81
Internal medicine	72
ENT	67
Neurotology	14
Cardiology	8
Opthalmolgy	5
Psychiatry	4
Rheumatology	4
Neuroradiology (MRI)	4
Immunology	2
Physiotherapy	2
Angiology	1
Other	16

Comparing the subsequent diagnosis with the documented diagnosis in the ED, in only 44 patients (14.3%) the diagnosis was agreeing, and in several cases that was of BPPV cause.

For statistical view, the diagnosis was divided into two groups: vestibular and extravestibular. Cohen's Kappa test was used for statistical evaluation.

Vestibular disorder group includes MD, vestibular neuritis, BPPV, and other vestibulopathies. Extravestibular disorder group includes CVD, internal medicine causes for dizziness.

In the studied population, 244 patients (79.2%) complained of dizziness as a leading symptom, and 64 patients (20.8%) had comorbidities of some medical condition (arrhythmia, cardiac or cerebral infarction, hypertension, carotid atherosclerosis).

Table 6. ED diagnosis and later diagnosis comparison (Kappa test). For analysis we categorised the diagnosis as vestibular - extravestibular disorders [115].

	Based on ED vestibular disorder	**Based on ED extravestibular disorder**
Based on later examination vestibular disorder	122	13
Based on later examination extravestibular disorder	56	117

According to the result of the test, kappa = 0.560, which is a moderated relation according to the interpretation of the test (moderated: 0.41 - 0.60). Even if simplifying the results of Table 6., when comparing the diagnosis based on larger diagnostic collection groups, the correlation is moderated, consequently not very explicit.

Key point also of the study, was the analysis of the DHI questionnaires, as this results in information about the everyday life of patients. Total DHI values were

compared between three groups based on the duration spent to final diagnosis (days, weeks, months or one year). For the clearance of the final diagnosis, days (28.8%) was reported in the most cases, then weeks (24.2%). However, it should be noted that in 24.02% of cases definitive diagnosis was missing. The patients were further divided into two groups (given diagnosis - not given diagnosis), in order to see these results on the impact on QoL. Mann-Whitney U test ($p = 0.044$) showed significant difference between the two groups of total DHI scores, pointing out that in the absence of diagnosis and adequate treatment, the QoL of patients is significantly reduced.

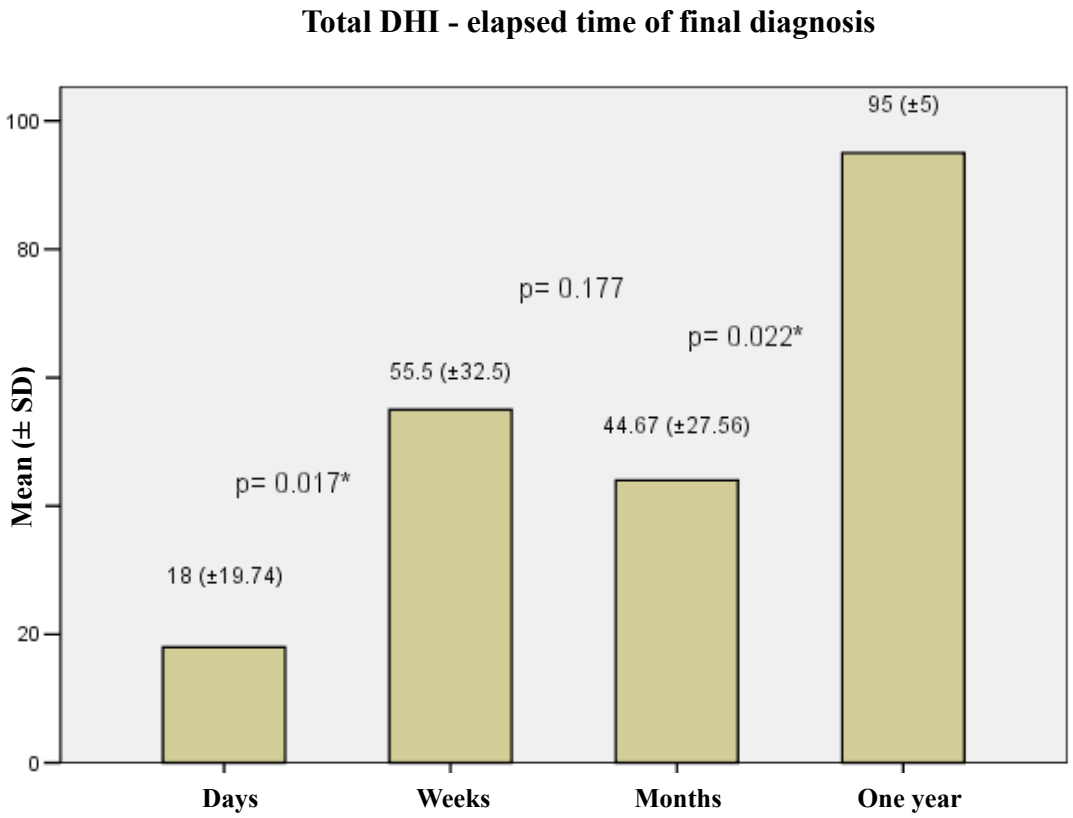

Figure 15. Distribution of total DHI values by time of diagnosis. Parameters show mean and SD values. P values were determined using Mann-Whitney U test, *: statistically significant difference [115].

According to Figure 15., in most cases, the value of deterioration in QoL increases proportionally with time to diagnosis, as indicated by the mean values and p values for each group [115].

4.2. Assessment of the patients' quality of life visiting the Emergency department with dizziness

According to the ED documentation the vertiginous population was generally categorized into peripheral vestibular lesion (37%), central vestibular lesion (29.5%) and population with no diagnosis (24.02%). As shown in the Figure 16., the duration of the dizziness episode in predominance was seconds, followed by days and hours of vertigo lasting. The duration of vertigo episodes is typical for some of the disorders, vertigo lasting for seconds is often seen in BPPV, minutes or hours in MD, one day or several days in vestibular neuritis and constant disequilibrium mostly occur in CVD. Because of the high incidence of BPPV the findings can be explained, although the second and third most frequent groups of hours and several days, are of greater importance, since the long-lasting episodes impact negatively the everyday life of a patient.

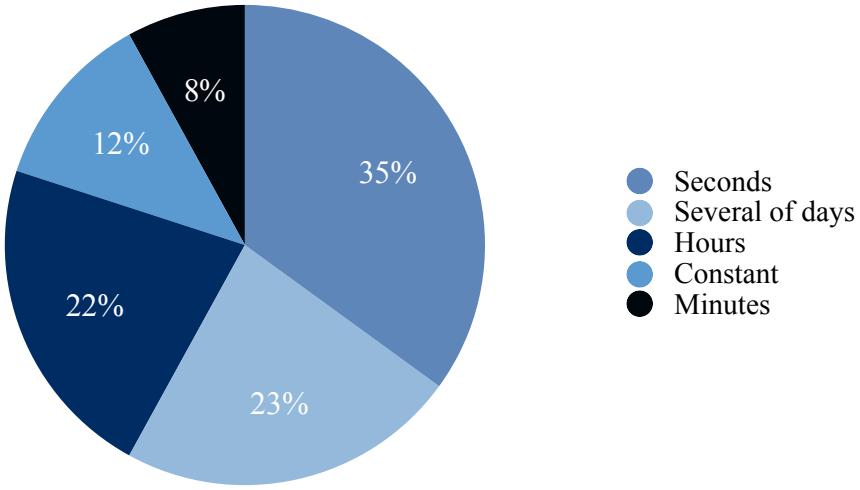

Figure 16. Duration of vertigo attacks based on patients' answers. (Maihoub S, Molnár A, Csikós A, Kanizsai P, Tamás L, Szirmai Á. (2021) Assessment of the patients' quality of life visiting the emergency department with dizziness. Orv Hetil, accepted for publication).

Along with the sudden dizziness, patients in most of the cases had accompany symptoms and complains. Based on the questionnaire the most frequent one was nausea, which is often seen as vegetative symptom in all types of vestibular lesions (Table 7.). All of the accompanied symptoms could have an effect on the QoL, but nausea and vomiting more remarkably, since these symptoms exert a strong effect on the everyday life.

Table 7. Dominant complaints accompanying vertigo attack. (Maihoub S, Molnár A, Csikós A, Kanizsai P, Tamás L, Szirmai Á. (2021) Assessment of the patients' quality of life visiting the Emergency department with dizziness. Orv Hetil, accepted for publication).

Accompanied symptoms	% of patients
Nausea	27
Headache	21
Tinnitus	17
Vomiting	17
Hearing loss	11
Syncope	7

Statistical analysis was carried out based on the result of the DHI questionnaire. Patients were divided into two groups as follows: patient referred to neurotologic examination or not, and the total DHI scores were contrasted. According to Figure 17. there was no statistically significant difference between the two groups ($p = 0.97$). This result could be explained by the fact that neurotologic examination was not performed in justified cases. Cases, such as CVD, rheumatological, internal medicine pathologies as well as cardiological disorders were referred to the neurotology, consequently the outcome of the statistical analysis was not the one expected (i.e. no significant difference between the two DHI groups). Moreover, the neurotology examination in some cases was based on the patient's decision, and not based on the necessity of it.

Concluding based on these findings, it may have occurred that the DHI values of the two groups did not differ significantly. In accordance with the ED final diagnosis in well-founded cases (BPPV: 14, vestibular neuritis: 3, MD: 1) neurotologic examination was carried out in only 23.5% of the cases, and ENT examination was performed in only 35.3% of the cases.

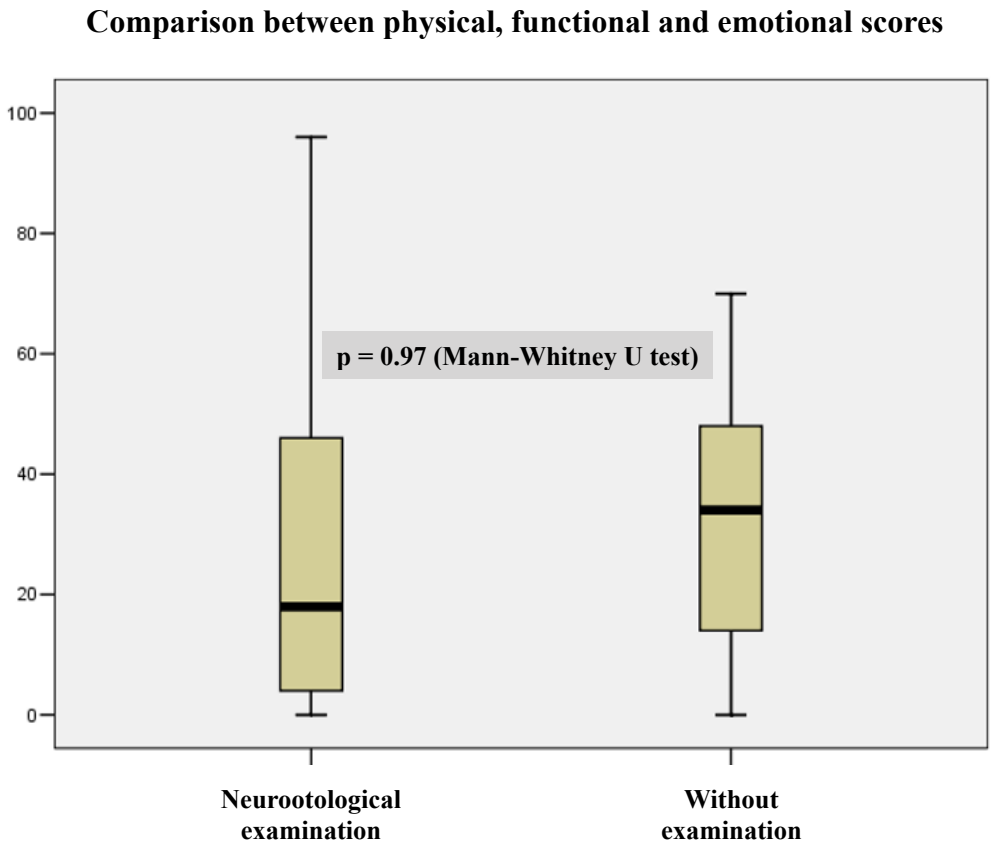

Figure 17. Relationship between the total DHI score and the neurootological examination. A box could be lower or higher than another; this could indicate a difference. Interpretation: the median value is shown by the line, which divides the boxes into two parts. The box represents the 50% of the data, and the whiskers are showing the lower and upper 25%, excluding outliers. (Maihoub S, Molnár A, Csikós A, Kanizsai P, Tamás L, Szirmai Á. (2021) Assessment of the patients' quality of life visiting the Emergency department with dizziness. Orv Hetil, accepted for publication).

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The development of QoL was analyzed in relation to the time taken for appropriate examination and diagnosis in relation to the onset of symptoms. Comparing the patients total DHI, as seen in Table 8., a statistically significant difference was seen between days and weeks, which strengthened the hypothesis were a higher total DHI score is correlated with a poorer QoL in the case of a later diagnosis.

Table 8. Comparison of total DHI as a function of time to diagnosis. (Molnár A, Csikós A, Kanizsai P, Tamás L, Szirmai Á. Assessment of the patients' quality of life visiting the Emergency department with dizziness. Orv Hetil, accepted for publication).

Time to diagnosis	Mean ± SD	p values (Mann-Whitney U test)
Days	18 ± 2	p = 0.01*
Weeks	55 ± 33	
		p = 0.2
Months	44.7 ± 3	
		p = 0.03*
A year	95 ± 5	

By analyzing the DHI answers of the patient we were able to make a comparison between the physical (P), functional (F) and emotional (E) question scores. Based on the boxplots there was a difference seen between P, F and E scale scores of the patients, indicating that the highest values were found in the P score group (Figure 18.). According to statistical analysis there was a statistically significant difference detected between P and F ($p < 0.00001$), P and E subgroups ($p = 0.00022$), however between F and E scores there was not ($p = 0.56$). Questions in P category include everyday tasks, such as looking towards a direction, walking down a sidewalk, performing ambitious activities, turning over in bed. Since this area is affected the most, we could see the deterioration of the other areas increasing simultaneously.

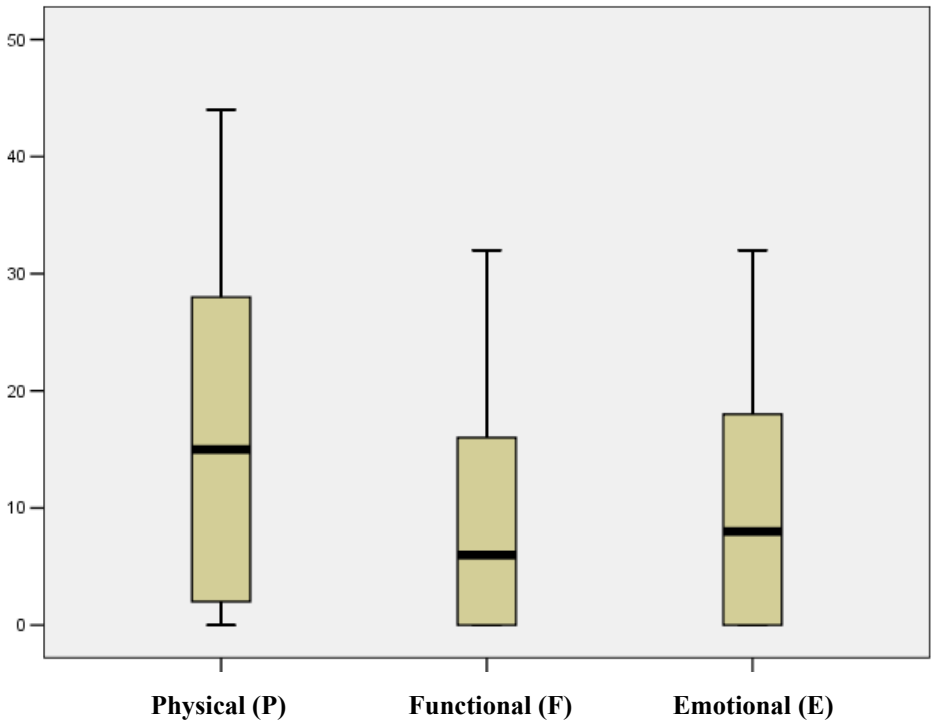

Figure 18. Boxplot of DHI questionnaire results. (Maihoub S, Molnár A, Csikós A, Kanizsai P, Tamás L, Szirmai Á. (2021) Assessment of the patients' quality of life visiting the Emergency department with dizziness. Orv Hetil, accepted for publication).

4.3. Different stages in Ménière's disease based on US-COMP-CCG

MD is divided into stages according to the severity and frequency of the symptoms. The determination of the stage, therefore, may be a useful tool to use for treatment strategy and improvement of a patients QoL [117].

By analyzing the patients' results, the distribution was the following: 14 patients (33.3%) were categorized in stage I, 15 patients (35.7%) in stage II, and 13 patients (30.9%) in stage III. Among the control patients, no significant difference was detected in US-COMP-CCG results compared with other statokinetic balance tests. All p values were determined using Mann-Whitney U test.

Parameters of the Standing Test

Analyzing these parameters, we found that all of the parameters of the US-COMP-CCG tests are pathological in MD (Table 9., $p < 0.05$). The longitudinal sway

parameter shows that the difference in the mean values between the normal and all MD patient groups differ statistically significant (p = 0.047). In the lateral sway, the normal value was substantially different from the pathological values. The increasing values showed the deteriorating vestibular system; the difference in the mean values were of significance (p = 0.003). There was also no correlation between the parameters of normal and MD patients (Spearman rank: 0.92, p = 0.517). The forehead covering area was increasing with the staging progression, showing severe imbalance in an advanced MD stage clinically and statistically. All groups showed statistically significant difference (p = 0.003), especially between the results in stage III patients compared to the normal values (p < 0.0001) according to Mann-Whitney U test (Spearman rank: 0.117, p = 0.525). However, the sensitivity of forehead covering area was low in stage III (ROC analysis, AUC: 0.328, TPR: 32.8%). The torticollis angle parameter showed lower values in the patients suffering from the disease than in the normal patients, but the difference was not statistically significant (p = 0.65), and there was also a correlation between the normal and pathologic parameters (Spearman rank: 0.380, p = 0.032), which means that the difference between the parameters of the normal group and MD was not significant.

Table 9. Values of standing test parameters (**mean ±** SD) in the different groups.
*Torticollis angle results were given in absolute value, without direction [117].

	All MD patients	**Stage I**	**Stage II**	**Stage III**	**Normal system**
Longitudinal sway (cm)	**9.42** ± 4.78	**7.58** ± 3.07	**8.36** ± 4.06	**10.98** ± 6.36	**6.52** ± 2.06
Lateral sway (cm)	**5.89** ± 3.4	**4.93** ± 2.4	**5.9** ± 3.73	**6.54** ± 3.63	**3.53** ± 1.17
Forehead covering area (cm^2)	**79.06** ± 79.63	**98.35** ± 94.13	**82.6** ± 85.12	**63.04** ± 62.86	**23.1** ± 11.69
Torticollis angle* (degree)	**12.76** ± 9.81	**10.11** ± 8.37	**14.67** ± 12.9	**53.42** ± 23.99	**9.31** ± 5.33

Parameters of the Stepping Test

The stepping test parameters showed different results from each other (Table 10., $p < 0.05$). The longitudinal deviation value was substantially lower in normal vestibular patients (mean ± SD: 60.65 ± 16.43) compared to that of stage I (66.29 ± 18.19, $p = 0.32$) and stage II (63.24 ± 42.75, $p = 0.55$) patients, whereas stage III patients are unexpectedly near normal (53.41 ± 23.99, $p = 1.13$). The differences were not of significant change. In the lateral sway width parameter, the value was increasing according to stage progression, as we often see in clinical practice during the examination of MD patients, but the results showed no statistical significance ($p = 1$). Angular deviation met the clinical expectations only in stage I. By comparing the normal and all MD patient groups, the difference in the mean values showed statistical significance ($p = 0.013$). In the self spin parameter, the normal results are different from the pathological values only in the stage II patients, and the difference was statistically significant ($p = 0.0001$). Spearman correlation also suggested statistically significant difference (Spearman rank: 0.063, $p = 0.656$). This parameter seems to be the most sensitive in the objective staging (ROC analysis, AUC: 0.962, TPR: 96.2%) [117].

Table 10. Values of stepping test parameters (**mean** ± SD) in the different groups. **Angular deviation and self spin results were given in absolute value, without direction [117].

	All MD patients	**Stage I**	**Stage II**	**Stage III**	**Normal system**
Longitudinal deviation (cm)	**60.1** ± 22.08	**66.29** ± 18.19	**63.24** ± 42.75	**53.41** ± 23.99	**60.65** ± 16.43
Lateral sway width (cm)	**14.83** ± 4.76	**14.1** ± 3.78	**13.38** ± 4.1	**16.47** ± 5.69	**15.73** ± 6.8
Angular deviation (degree)**	**147.9** ± 28.62	**164.45** ± 10.3	**146.95** ± 28.06	**137.28** ± 36.74	**163.78** ± 13.13
Self spin (degree)**	**50.65** ± 37.24	**41.33** ± 27.98	**62.4** ± 43.04	**47.64** ± 38.42	**35.57** ± 29.62

4.4. Intratympanic steroid therapy for advanced MD in correlation with the vestibular system

Based on the baseline parameters the two groups were appropriate to compare (Table 11.), since there was no statistically significant difference detected between the parameters of the two groups [118].

Table 11. Baseline parameters for the two groups (group 1: treated with ITS, group 2: control group). For all US-COMP-CCG parameters **mean** ± SD values were included. [a]: Chi square test, [b]: Mann-Whitney U test [118].

	Group 1	**Group 2**	**p value**
Gender (male / female)	16 / 22	33 / 49	0.85[a]
Age (mean ± SD)	**55.62** years ± 9.46	**52.08** years ± 12.25	0.99[b]
Side of MD (right / left)	22 / 14	43 / 39	0.38[a]
Longitudinal sway (cm)	**8.44** ± 3.32	**9.62** ± 4.42	0.53[b]
Lateral sway (cm)	**6.24** ± 2.62	**6.17** ± 3.33	0.57[b]
Forehead covering area (cm$^{2)}$)	**60.40** ± 47.00	**104.72** ± 124.73	0.28[b]
Torticollis angle (degree)	**8.75** ± 4.60	**10.14** ± 5.53	0.87[b]
Longitudinal deviation (cm)	**63.85** ± 24.22	**66.63** ± 20.88	0.23[b]
Lateral sway width (cm)	**16.35** ± 5.46	**14.78** ± 4.11	0.24[b]
Angular deviation (degree)	**159.81** ± 20.42	**156.90** ± 20.04	0.33[b]
Self spin (degree)	**41.70** ± 31.30	**56.94** ± 42.68	0.38[b]

All MD patients showed a moderate to severe hearing loss, prolonged and frequent vertigo attacks and instability. Changes in at least 2 parameters in the standing

test were observed in 6/38 patients and in the stepping test, changes were observed in 13/38 patients. To examine whether there is a change after ITS treatment in the US-COMP-CCG parameters or not two analyses were carried out: parameters before and after the therapy, and parameters of patients treated with ITS and of control group were contrasted. The results of the standing test before and after treatment are shown in Figure 19.

Parameters of standing test before and after ITS treatment

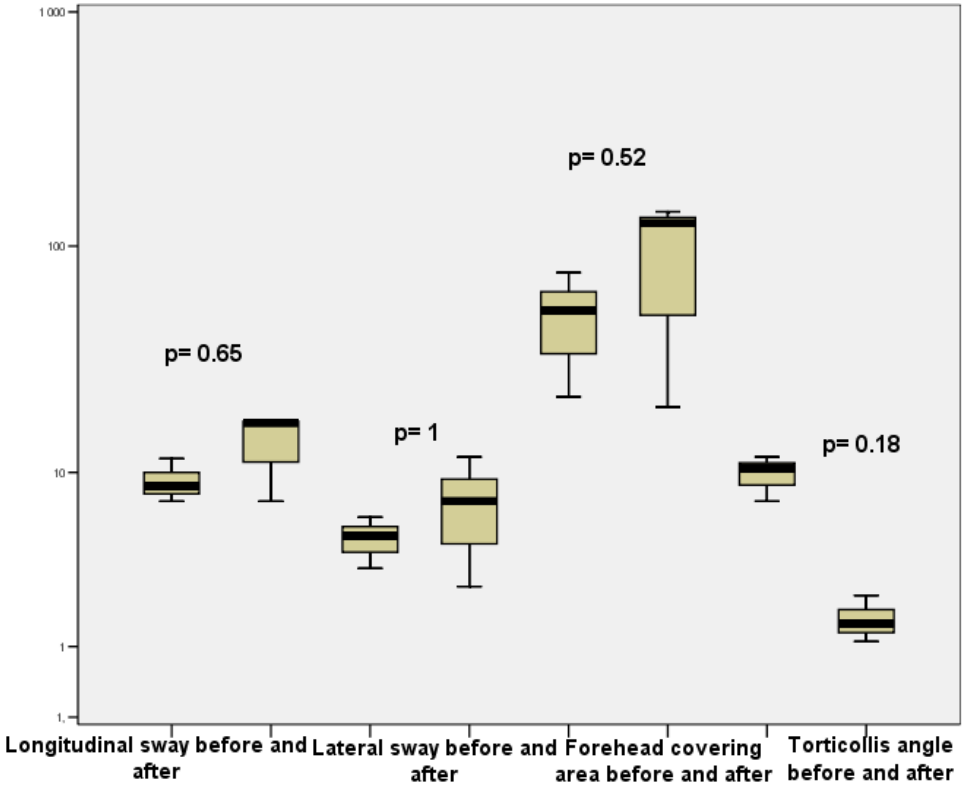

Figure 19. Boxplot about the parameters of the standing test before and after treatment. P values were determined based on the Mann-Whitney U test [118].

As shown in Figure 19, based on the boxes, there is no obvious difference between the parameters before and after treatment, and the p values also indicate no significant difference between the pre- and post-treatment parameters. Based on the analysis it can be stated the ITS therapy has no significant effect on the outcome of the standing test.

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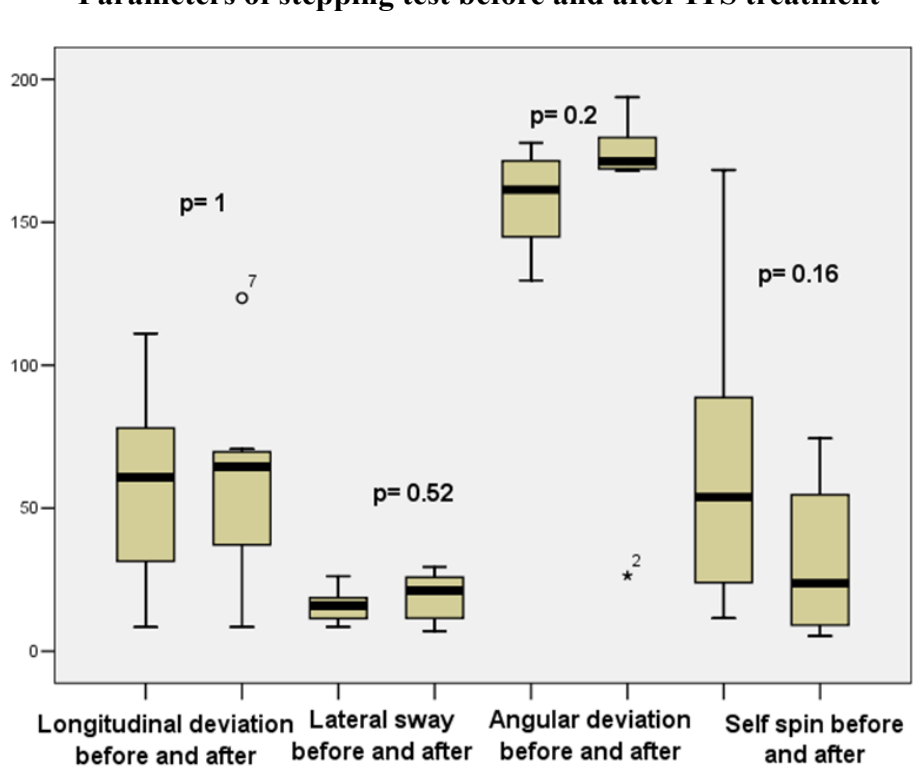

Figure 20. Boxplot about the parameters of the stepping test before and after treatment. P values were determined based on the Mann-Whitney U test [118].

The results of the stepping test are shown in Figure 20. Whereas, in the case of the stepping test, no obvious difference between the boxes of pre- and post-treatment values can be detected, and the p values also do not indicate a statistically significant difference between the parameters. Thus, that ITS does not have a significant effect on the outcome of the stepping test. The results of control patients (i.e. patients who were not treated with ITS) and of those treated with ITS were analyzed and contrasted as well. The results are shown in Figure 21.

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Parameters of standing test of controls and of those treated with ITS

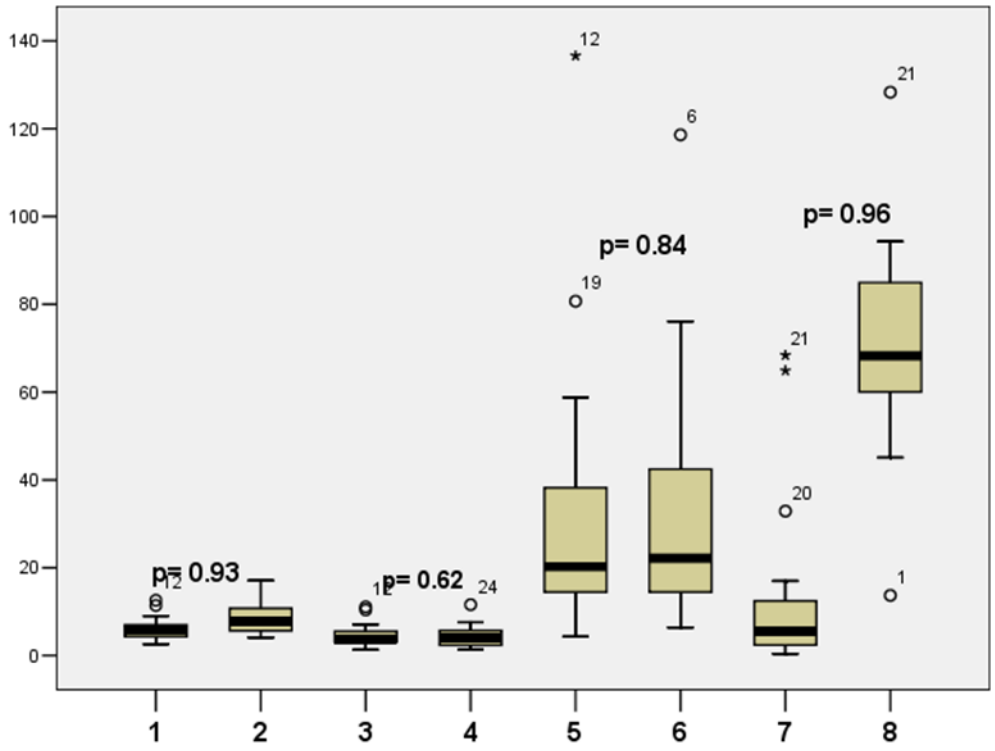

Figure 21. Comparison between the parameters of the standing test of controls and patients treated with ITS. P values were determined based on the Mann-Whitney U test. 1: Longitudinal sway of treated patients, 2: control, 3: Lateral sway of treated patients, 4: control, 5: Forehead covering area of treated patients, 6: control, 7: Torticollis angle of treated patients, 8: control [118].

Based on the boxplot, it can be concluded that when parameters of controls and treated MD patients were contrasted, there was no difference between the boxes in most cases, and the difference, if any, was determined not to be statistically significant. The same results came up in the stepping test (Figure 22.), in which case the median values and the boxes of parameters did not differ and based on the p values no significant difference was detected.

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Parameters of stepping test of controls and of those treated with ITS

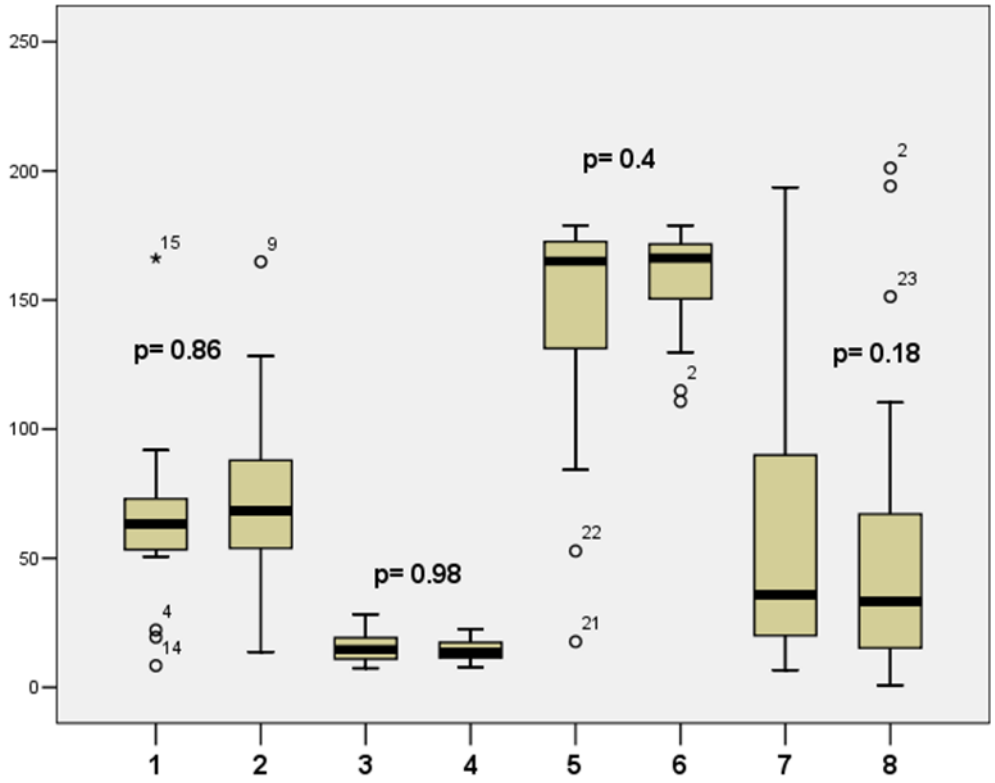

Figure 22. Comparison between the parameters of the stepping test of controls and patients treated with ITS. P values were determined based on the Mann-Whitney U test. 1: Longitudinal deviation of treated patients, 2: control, 3: Lateral sway width of treated patients, 4: control, 5: Angular deviation of treated patients, 6: control, 7: Self spin of treated patients, 8: control [118].

Further analysis was made based on the Kaplan-Meier curve and logistic regression to strengthen the results and to make the long-term follow-up possible since all of the US-COMP-CGG examinations performed on each patient could be taken into consideration. Based on the survival-ship curve (Figure 23.), there was no visible difference between the two curves (e.g. significantly worsened outcome of US-COMP-CGG of control and patients treated with ITS), and the logistic regression also indicated [p = 0.445; Odds ratio: 1.654 (95% CI: 0.166 - 0.197)] that there was no significant difference between the results of the groups [118].

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US-COMP-CCG outcomes before and after IT dexamethasone treatment

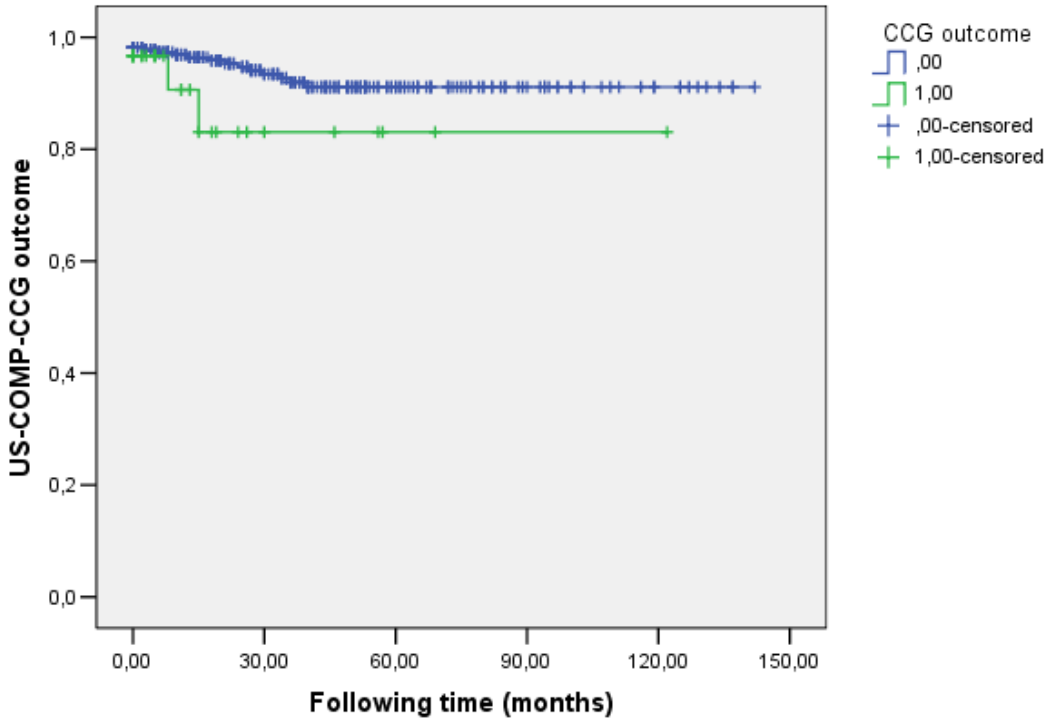

Figure 23. Occurrence of worsened US-COMP-CCG parameters before and after ITS treatment. In SPSS the number of events (i.e. worsening in US-COMP-CCG parameters) that happened at time (following time) was determined as follows: 0, if less than 2 parameters and 1, if more than 2 parameters showed aberration. Blue: not treated, green: treated [118].

4.5. Differentiation between idiopathic BPPV and secondary BPPV based on the US-COMP-CCG results

Parameters of standing and stepping were collected for each patient and mean ± SD parameters were also calculated (Table 12.). Based on the results of the difference between the mean values of the parameters of control and i-BPPV and s-BPPV groups the possible diagnostic role of two parameters was brought up: forehead covering area and self spin [44].

To contrast the results of normal patients and of those involved in BPPV, Mann-Whitney U test was used. As shown in Table 12. in case of i-BPPV there was no

statistically significant difference between the two groups. In the s-BPPV group statistically significant difference was detected in case of forehead covering area ($p = 0.005$) and self spin ($p = 0.025$) parameters. So, the difference, which was seen according to the mean values, was supported statistically.

Categorical analysis (i.e. correlation between pathologic US-COMP-CCG parameter and positive final result of complete neurotological examination/normal parameter and negative final result) was carried out too (Fisher exact test). In case of forehead covering area parameter of s-BPPV patients the p value was determined as 0.037, which implies a statistically significant result, but when calculation for i-BPPV patients was carried out, no significant difference was detected ($p = 0.076$). In case of self spin parameter similar results came up (s-BPPV: strong difference, $p = 0.00001$, i-BPPV: 0.32, not significant).

Forehead covering area and self spin parameters remark the severe imbalance in s-BPPV clinically and statistically. This could be explained by the fact that patients experiencing s-BPPV have a more damaged balance system due to the involvement of a primarily affected vestibular disorder, such as in vestibular neuritis, or in advanced MD.

Table 12. Normal ranges of US-COMP-CCG parameters and **mean** ± SD values for each test of i-BPPV, s-BPPV and control patients. ***** indicates statistically significant difference [44].

	Normal system	**i-BPPV**	**p value (Mann-Whitney U test)**	**s-BPPV**	**p value (Mann-Whitney U test)**
Longitudinal sway (cm)	**8.3** ± 2.8	**2.56** ± 2.56	0.32	**9.45** ± 4.41	0.56
Lateral sway (cm)	**4.2** ± 1.73	**3.99** ± 1.32	1.27	**5.35** ± 3.32	0.72
Forehead covering area (cm^2)	**49.5** ± 41.02	**34.7** ± 20.67	0.18	**186.49** ± 278.73	0.005*
Torticollis angle (degree)	**8.84** ± 5.56	**8.56** ± 5.25	0.69	**8.2** ± 4.77	0.88
Longitudinal deviation (cm)	**67.38** ± 21.87	**67.97** ± 22.26	0.84	**69.66** ± 27.69	0.88
Lateral sway width (cm)	**16.42** ± 7.05	**15.36** ± 6.04	0.04	**15.94** ± 6.54	0.63
Angular deviation (degree)	**165.27** ± 10.98	**163.53** ± 13.03	0.88	**161.17** ± 17.12	0.33
Self spin (degree)	**44.43** ± 33.15	**35.07** ± 27.21	0.05	**86.33** ± 78.16	0.025*

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Self spin and forehead covering area parameters of i-BPPV and s-BPPV patients were also contrasted using boxplots. Although comparison of forehead covering ($p = 0.44$) and self spin ($p = 0.16$) parameters did not show significant difference, as shown in the boxplots (Figure 24, 25.) difference between the groups exist.

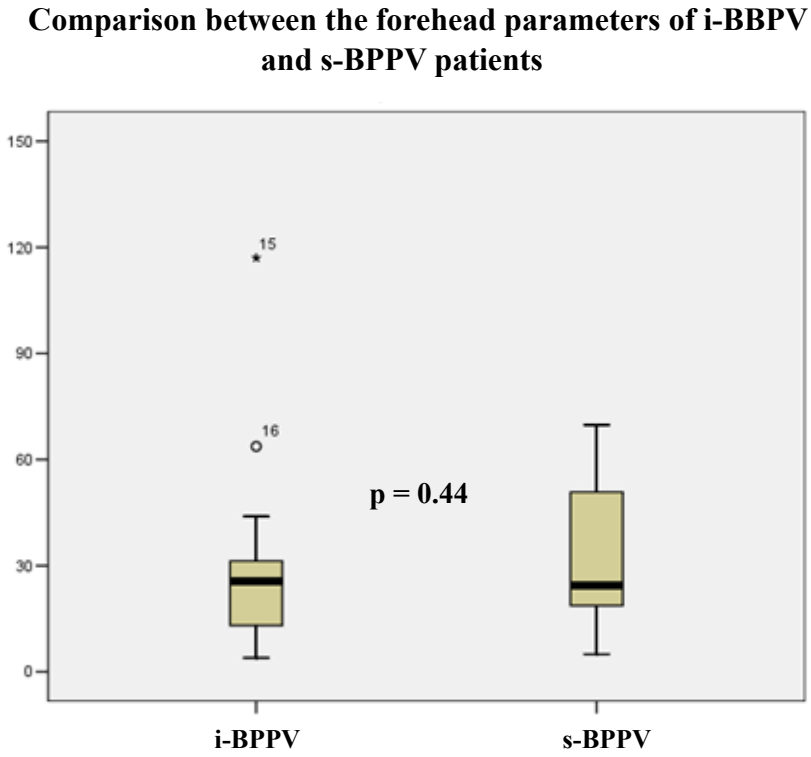

Figure 24. Comparison between forehead covering area parameter values of i-BPPV and s-BPPV patients [44].

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Comparison between the self spin parameters of i-BBPV and s-BPPV patients

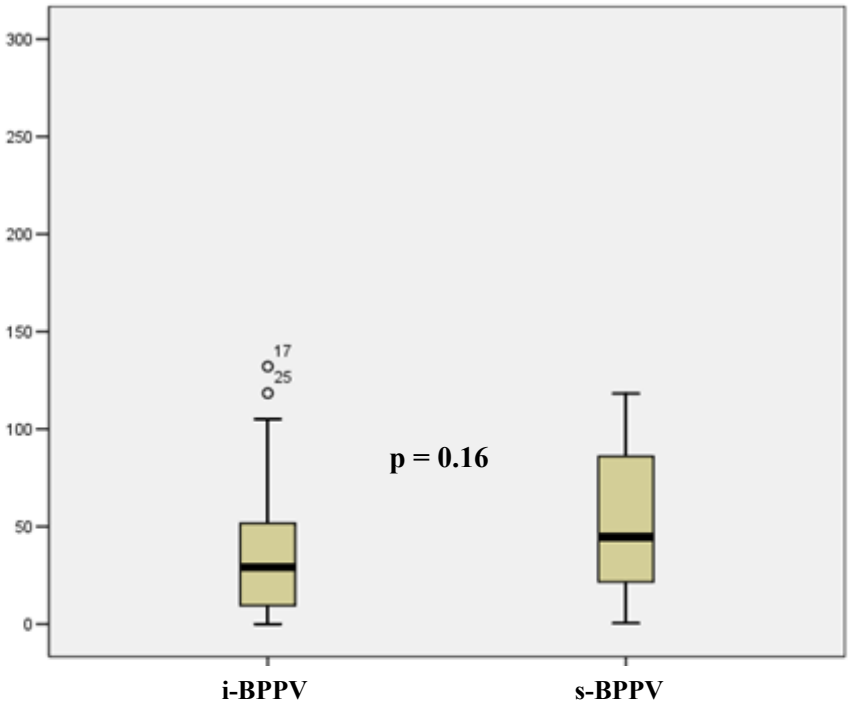

Figure 25. Comparison between self spin parameter values of i-BPPV and s-BPPV patients [44].

To determine the true positive (TPR) and negative (TNR) rates of the parameters ROC curves were drawn (Figure 26.) and specificity and sensitivity were calculated using AUC. Our analysis indicated that self spin parameter is highly sensitive (TPR: 67%) and specificity wise is also high (TNR: 76%). The forehead covering area parameter showed lower sensitivity (TPR: 29%), but a higher specificity (TNR: 57%).

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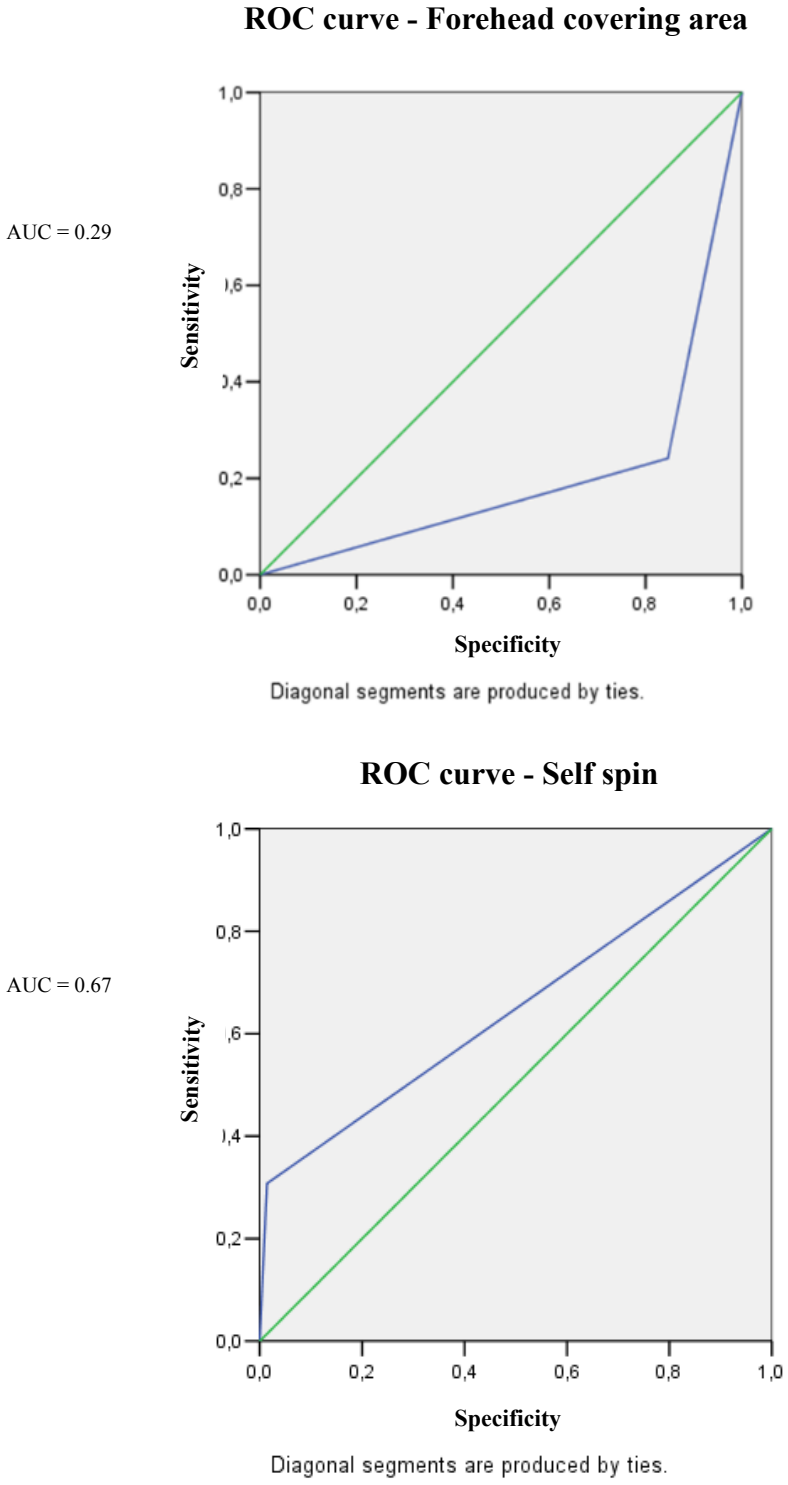

Figure 26. ROC curves for self spin and forehead covering area parameters. Green line is the reference line (50%), whereas the blue line is the data curve (parameters were calculated based on AUC) [44].

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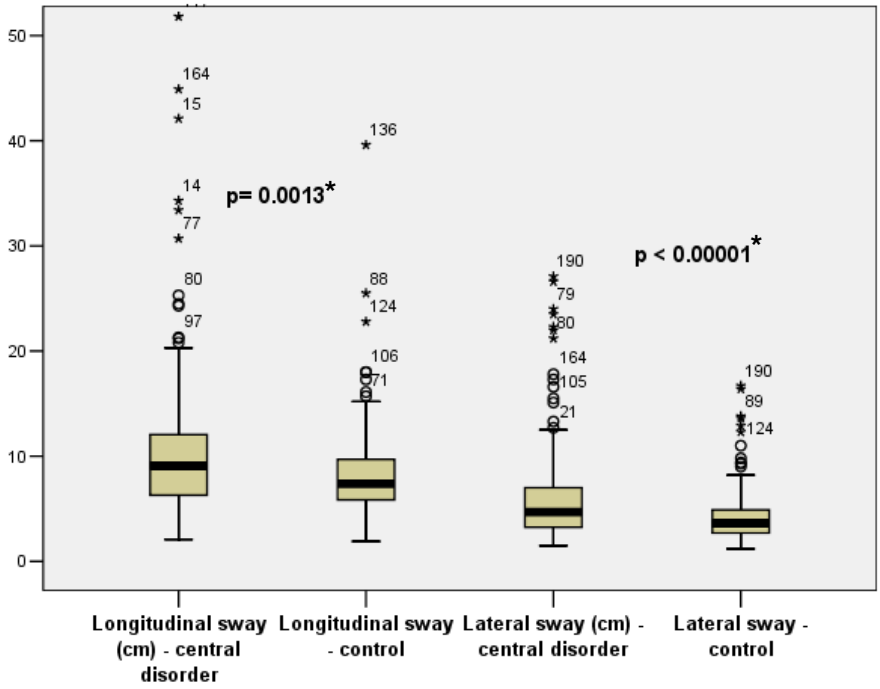
4.6. The diagnosis of central vestibular disorder based on the complementary examination of the vestibulospinal reflex

To determine which parameter of US-COMP0CCG could be specific for central vestibular disorders based on the gait dysfunctions, boxplots were drawn, and the parameters were contrasted to the results of the control group.

Standing test - Longitudinal sway and Lateral sway



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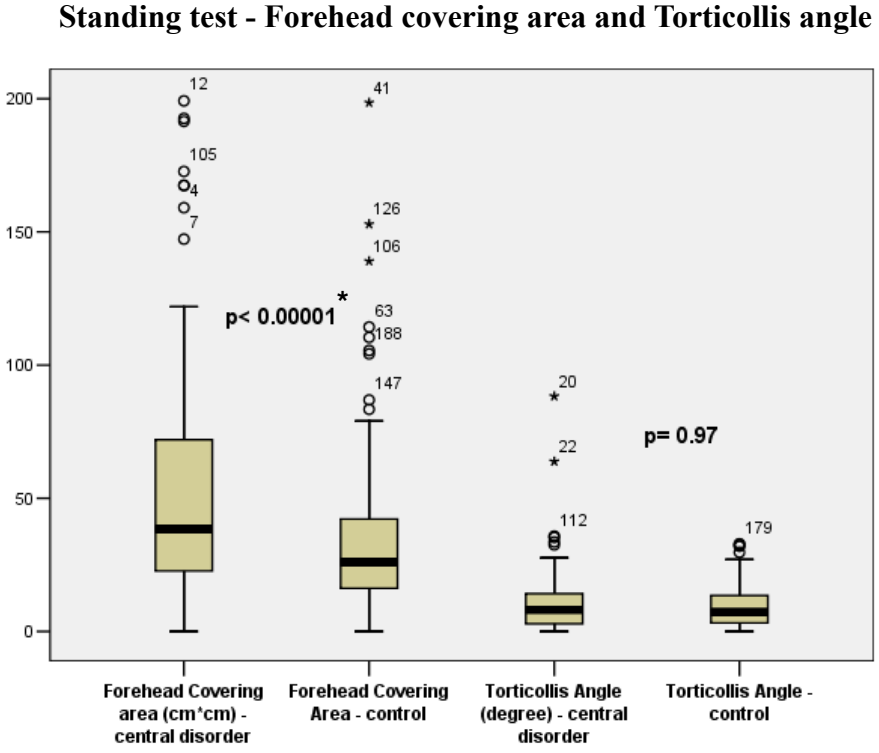

Figure 27. Boxes showing the parameters of standing test. The results of the non-parametric test are also included,* indicates statistically significant difference.

According to Figure 27., the boxes of longitudinal sway, lateral sway and forehead covering area parameters of standing test of central vestibular disorder group are showing higher values than those of the control group, indicating a difference between the parameters, and the results are statistically significant, suggesting a strong difference between the two groups. However, in case of torticollis angle parameter no obvious difference could be seen, which is also confirmed based on the statistical analysis ($p = 0.97$). These two facts indicate that the patient suffering from central vestibular disorder will not exhibit a deviation to the sides but rather a movement of body from back to front with tendency of increased unsteadiness and increased fall rate.

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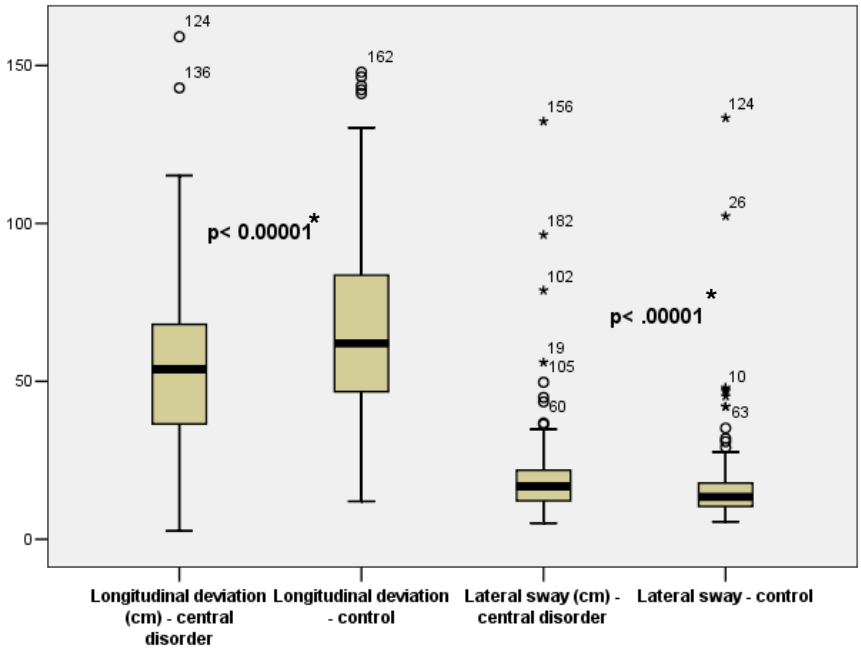
Stepping test - Longitudinal deviation and Lateral sway width



Stepping test - Angular deviation and Self spin

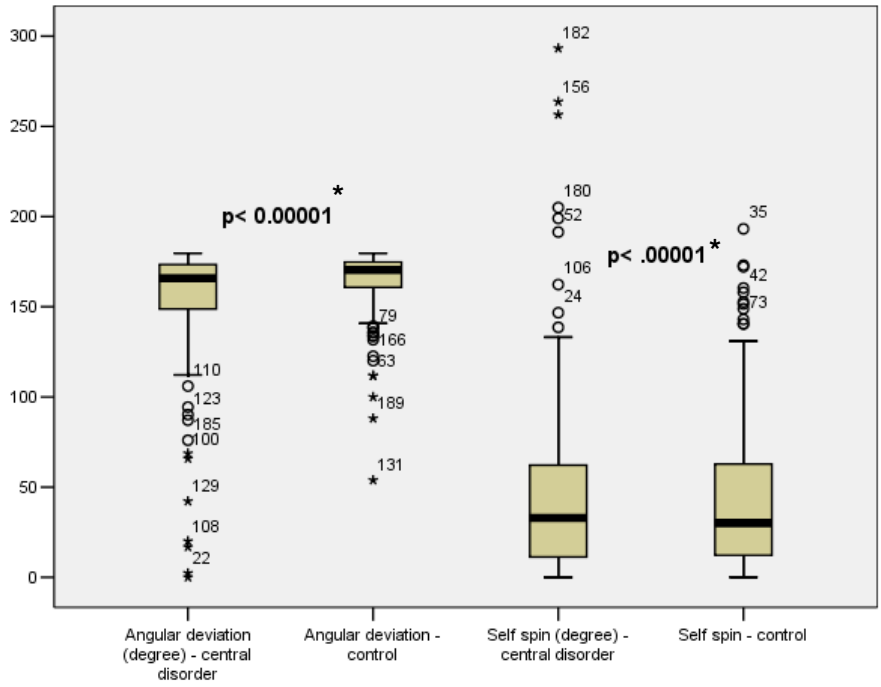


Figure 28. Boxes showing the parameters of stepping test. The results of the non-parametric test are also included, * indicates statistically significant difference.

As shown in Figure 28., all boxes of the stepping test parameters of central vestibular disorder group are higher than those of the control group, and the statistical analysis also indicates a strong difference in all cases.

Based on the analysis, all parameters of the stepping test, and most parameters of the standing test (excluding the torticollis angle parameter) can be useful in the diagnosis of central vestibular disorders. To analyze how the US-COMP-CCG can differentiate the normal and pathologic patients, the outcome of the tests was contrasted to the outcome of the complete neurotologic examination. For the analysis, categorical analysis (i.e., based on the normal parameters of US-COMP-CCG, the examined patient was normal/not and based on complete neurotological examination belongs to the normal group or not) was carried out by Chi-square test. The results are shown in Table 13. Normal parameters were based on our previously published data (see the material and methods section).

Table 13. Results of the categorical analysis. The * indicates statistically significant difference. (Data from our clinical material).

Parameters	Chi-square test p value
Longitudinal sway (cm)	< 0.00001*
Lateral sway (cm)	< 0.00001*
Forehead covering area (cm^2)	0.0001 *
Torticollis angle (degree)	0.55
Longitudinal deviation (cm)	0.05 *
Lateral sway width (cm)	0.011*
Angular deviation (degree)	0.20
Self spin (degree)	0.63

Based on Chi-square test correlation between the result of US-COMP-CCG (normal/pathologic value) and final results were detected in cases of longitudinal sway, lateral sway, forehead covering area parameters of standing test, and of longitudinal

deviation and lateral sway width parameters of stepping test. Irrevocably, it can be concluded that even though there is significant difference between most parameters of control and central disorder groups, categorical analysis indicates that standing test is more specific for central vestibular disorders, since most of the parameters showed similar results contrasted to the other neurotologic examinations.

According on area under curve of ROC curves, specificity and sensitivity parameters for each test were determined (Table 14.). As shown, parameters of standing test are more specific, while parameters of stepping test are more sensitive. Based on the analysis, the highest specificity was detected in case of lateral sway parameter of standing test (96.5%, which is almost a perfect parameter) and the most sensitive parameter is the angular deviation of the stepping test (98.9%). This fact indicates the necessity to combine the two examinations, and the most important parameters based on the analysis are the lateral sway and angular deviation parameters.

Table 14. Sensitivity and specificity parameters for each test.

Parameters	Sensitivity (%)	Specificity (%)
Longitudinal sway (cm)	46	76
Lateral sway (cm)	19.4	96.5
Forehead covering area (cm^2)	49.2	69.6
Torticollis angle (degree)	1.05	43.5
Longitudinal deviation (cm)	61.3	29.6
Lateral sway width (cm)	86.9	23.04
Angular deviation (degree)	98.9	0
Self spin (degree)	78.5	19.6

4.7. Comparative study between the auditory and vestibular functions in Ménière's disease

This study was made retrospectively, and the results of 43 patients with unilateral MD were investigated. The right ear was affected in 25 patients, and the left side in 18 patients [119]. Eight patients were classified into stage A, 11 patients into stage B, 19 into stage C, and 5 patients into stage D (Table 15.). For each MD stage the relationship of the PTA and responses of the CVT were examined too.

Table 15. Summary of the stages of MD, PTA and responses of CVT (**mean** ± SD) [119].

	Stage A	**Stage B**	**Stage C**	**Stage D**
Number of patients	8 (18.6%)	11 (28.6%)	19 (44.2%)	5 (11.6%)
PTA (mean dB ± SD)	**14.99** ± 7	**33.31** ± 5.37	**55.9** ± 8.31	**75** ± 3.91
CP% (mean dB± SD)	**37.25** ± 33.55	**40.5** ± 12.07	**39.21** ± 30.84	**41.6** ± 38.91

A shown in Table 15., most patients were included in stage C, and as the staging is based on the PTA the average thresholds are increasing with the stage, however, such a correlation in case of CP% is not unequivocal.

To analyze further correlation between the parameters, dot diagrams were included, and correlation tests were used. As shown in Figure 29., based on the linear correlation ($R^2 = 0.06$) there is no correlation between the examined parameters, which is also supported by Pearson correlation (rho = 0.244, p = 0.115), indicating no significant linear correlation between the two parameters. Examining the non-linear correlation using Spearman test, no significant correlation was detected either (rho = 0.245, p = 0.113).

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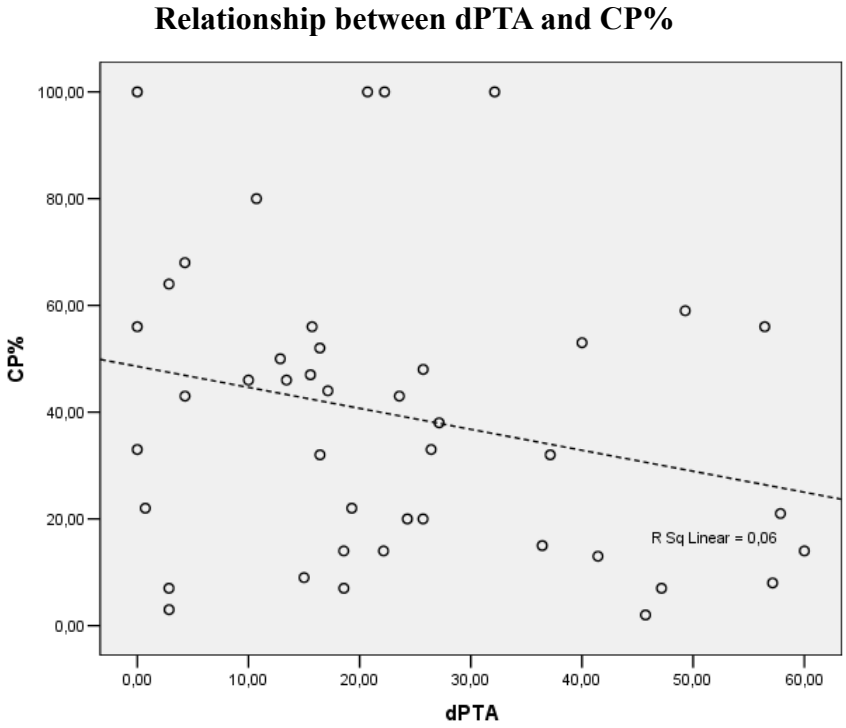

Figure 29. The analysis of CP% and dPTA (rho = 0.245, p = 0.113) [119].

To perform categorical analysis using Cohen's Kappa test, the dPTA and CP% parameters were subcategorised into a lesser and into a greater range as shown in table 16. Kappa test was performed for the achievement of the comparison of the CP% and dPTA (Table 16.), resulting in kappa = 0.174 (95% CI: 0.431 - 0.0883), stating a slight relation according to the interpretation of the test (slight: 0 - 0.2). Based on the categorical analysis it also can be stated that increasing in on one of the parameters does not mean increasing tendency in the other one as well.

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Table 16. CP% and dPTA comparison (Kappa test) [119].

	dPTA 20 dB >	**dPTA 20 dB <**
CP% 20 <	4 (9.3%)	13 (30.2%)
CP% 20 >	1 (2.3%)	25 (58.2%)

Comparison between PTA average of the diseased ear and the CP% was done. As shown in Figure 30., according to the linear correlation ($R^2 = 0.007$), there is no correlation between the examined parameters. Pearson correlation (rho = 0.085, p = 0.586) also supported this statement. Examining the non-linear correlation using Spearman test, no significant correlation was detected (rho = 0.11, p = 0.481).

Relationship between PTA of the involved cochlea and CP%

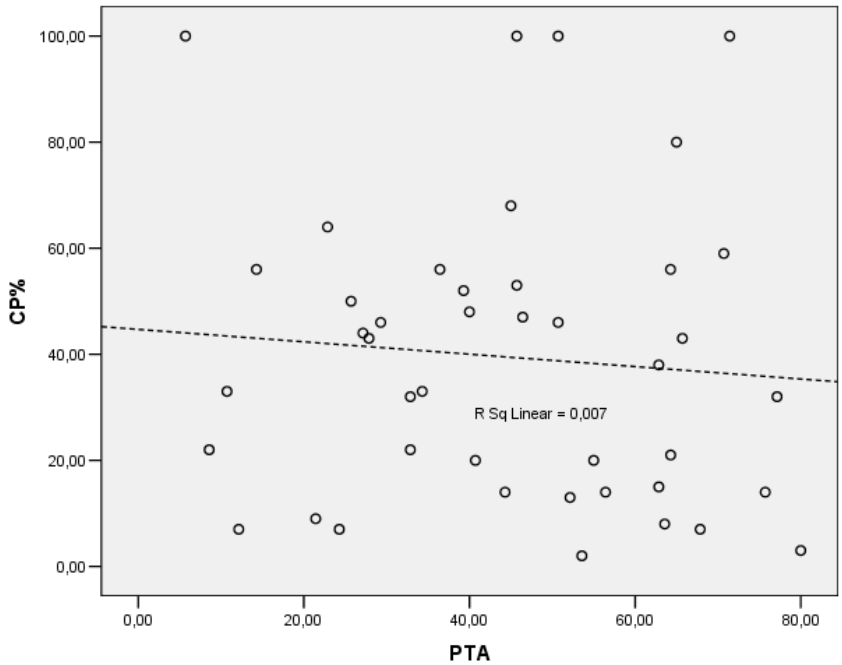

Figure 30. The analysis of CP% and PTA (rho = 0.11, p = 0.481) [119].

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The distribution of CP% parameters in different stages of MD are shown in Figure 31. Based on the boxplot it can be concluded that there is no significant difference between the parameters of the different stages, which was also strengthened by the statistical anaylsis. It can be concluded, that a higher stage based on audiometry does not mean increasing values in CP% parameter.

Comparison between CP% in the different AAO-HNS stages

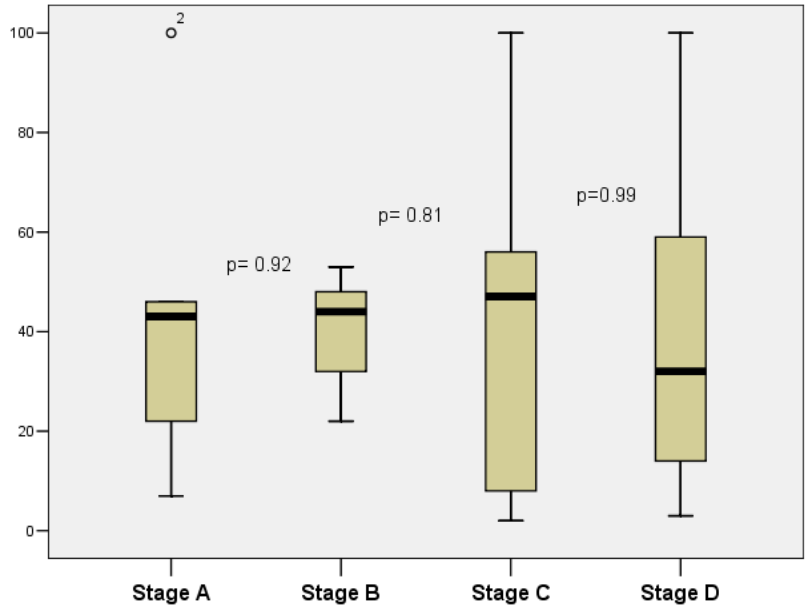

Figure 31. Comparison between CP% in the different AAO-HNS stages using Boxplot. P values were determined based on the Mann-Whitney U test [119].

Through the usage of the statistical analysis it is stated that no distinguished association exists between the hearing loss and the caloric reaction in the investigated frequencies. Meaning that a reduced caloric response can be obtained, disregarding the degree of hearing loss in the recorded frequencies [119].

5. Discussion

5.1. Emergency department diagnosis of the vertiginous population

The questionnaire was sent to all patients treated for dizziness/vertigo in the ED. There were more female patients among the responders of the returned questionnaires, and all age groups were present, however, on the basis of the average age, over 40s appeared, which is in line with everyday practice. For the other parameters, there was no significant difference between the proportion of respondents and non-respondents, so this can be considered as a representative sample. The proportion of questionnaires returned was a good indicator of the cooperative readiness of dizzy patients. However, it is important to emphasize that detecting the cause of dizziness is difficult even for a qualified person, so the use of questionnaires has a number of limitations. Diagnosis of dizziness, especially in therapy compliance, would be particularly important for the long-term cooperation of patients [115].

More contradiction was observed between the diagnosis in the emergency report and the information given to patients. Many patients did not receive any information, and many patients did not receive an explanation for the disease that was included in their written final report. Though, in today's computer world, a patient can immediately learn about the disorder named on the document, and if there is a discrepancy between the written and verbal diagnosis, it will completely confuse them. As a result, the patient becomes dissatisfied and an unclear diagnosis increases anxiety, which is common among dizzy population [122], especially if one possible diagnosis includes stroke [115].

Too much time elapsing between leaving the ED and the end of the examination process may also intensify the patient's anxiety, as evidenced by DHI score values and as a result deterioration in QoL. In order to perform further medical examinations an appointment is needed, whereas in a quarter of patients, this examination date would be several months later. Though among the examined population, approximately a quarter, did not receive a definitive diagnosis even when more tests were completed. A possible reason may be, that essential aspects of the medical history are overlooked or modified over time to reflect changes in the patient's condition, while the patient's condition is

constantly changing, improving, or worsening. At the same time the organic status may be improving, the psychological status deteriorates, and new symptoms may come to the forefront that have not seemed previously important [115].

By Varga et al. [123] it has been stated that 57% of the studied population did not have a definitive diagnosis, so in the rate of no diagnosis is showing an improving tendency, compared to previous studies. That seems to be a low diagnostic rate, however, the number of incorrect diagnosis is the same in the international literature as well [124]. To ensure the correct final diagnosis and differentiate between the several types of PVD complete neurotological examination is necessary. Out of the patients, only 14 underwent neurotological examination and only 67 patients underwent ENT examination. Although targeted examination of the vestibular system, along with other examinations, may help to clarify the cause of vertigo and imbalance, in the ED bedside testing is not a substitute. This is especially true for those disorders, which do not show typical symptoms after the acute phase (e.g. BPPV, vestibular neuritis), thus, subsequent retrospective examination provides valuable 'retrospective' confirmation of the diagnosis on the basis of valuable data obtained from emergency documentation (e.g. Dix-Hallpike maneuvre) [115].

Emergency diagnosis of dizzy patients is a major challenge for ED staff. It is a borderline issue, and due to the state of the patient not all examinations/tests are suitable at that moment. Nevertheless, the precise history taking and fast, targeted investigation may, in most cases, clarify the causative disorder. We would like to emphasize that accurate diagnosis is not a task of emergency care, but rather a subsequent medical examination, but the diagnosis of AVS requires immediate diagnosis, as it is essential to distinguish between central and peripheral cases. The concept of AVS was introduced by Hotson and Baloh in 1998 [108]. AVS is characterised by rapid onset of vertigo that lasts longer than 24 hours, along with spontaneous nystagmus, unsteady gait, and vegetative symptoms (nausea/vomiting) [114]. Isolated AVS is absent when the neurological symptoms are absent. The most common cause of AVS, is the vestibular neuritis, but also, for example, may be the posterior scala stroke, in which case differential diagnosis is particularly important and difficult task. According to the

literature, it is seen in 10-20% of patients in the ED. The second most common cause of AVS is ischemic stroke, of the cerebellum or brainstem [125]. It is important to note here that vertigo and nystagmus are the most common symptoms in patients with posterior scala stroke [126, 127]. A negative imaging result (computer tomography scan (CT), MRI) does not rule out the diagnosis of stroke, but one of the most reliable diagnostic procedures is the HINTS(+) test. With the help of HINTS(+) (Table 17.) it is possible to differentiate whether dizziness is of central or peripheral origin, but if it is peripheral dizziness, it is useful to specify which peripheral disease is involved. PVD include BPPV, vestibular neuritis, MD, vestibular migraine. After reviewing the emergency documentation, it was noticeable that the use of the HINTS+ test was not widespread in practice; the examining physician examines spontaneous nystagmus, statokinetic tests (Romberg's test, Bárány test) and possibly Dix-Hallpike maneuver, but that head impulse test and skew deviation test are not part of everyday routine. Instead of bedside examinations, they prefer the use of acute CT examination, although the sensitivity of HINTS(+) exceeds that of imaging examinations [114].

Table 16. HINTS(+) (head impulse test, nystagmus, test of skew, +: acute hearing loss) [115].

	Spontaneous nystagmus		**HIT**		**Skew-deviation**		**Possible acute hearing loss**
Vestibular neuritis (Peripheral)	Spontaneous nystagmus	+	Slow direction phase positive	+	No	+	No
Pseudo-neuritis (Central)	Gaze-evoked	and /or	Both direction negative	and/ or	Yes	and/ or	Yes

Highly always recommended, to properly inform the patient, that the dizziness may have been caused by involvement of the balance system, or in the absence of that, and that other possible causes (e.g. internal medicine disorders) exist. Moreover, the patient must be informed about every disorder we suspect, and what kind of specialist to consult, and the probability of the complaints to return with a recommended strategy. Therefore, the patient is well informed, knowing that there is further help for the existing health problem, and satisfied patients can also reduce the patient inflow in the ED in the long term [115].

5.2. Assessment of the patients' quality of life visiting the Emergency department with dizziness

Acute dizziness is a debilitating condition that can result in handicap [128, 129], and patients' self-awareness of QoL measurement is becoming a prime indicator for health care evaluation. Effects caused by a disease to the individual's QoL brings important information, both to an adequate diagnosis and to a forward therapy, since it gives details on the post-symptom evolution and the reflection in the physical, emotional and functional aspects [130].

According to our analysis we were able to establish that patients with even one acute episode of dizziness/vertigo scored greater than or equal to 30 on the DHI questionnaire. Based on DHI questionnaire literature, even with a minimum score achievement (10 points) further examinations are suggested [116]. Marking out those scores higher than 16 points, to be highly recommend for further examinations, such as referred to neurotology. However, in the cases of sending and examining patients suffering from other extravestibular and not vestibular causes, it results in time-consumption and not adequate treatment. Therefore, we would like to emphasize, that complete neurotological examination is necessary and highly recommended, but only in well-founded cases, which means PVD. To decide this, the method according to Szirmai can be used, who proposes a six 6-point questionnaire for the selection of patients in need of an neurotological examination [131].

All participating 308 patients had a physical complain, which this implies that all patients have a difficulty in everyday tasks, and the impact of it in the other areas, functional and emotional, varies. The physical aspects investigated by DHI, even though by fewer overall questions compared to other aspects of the questionnaire, were those counted with the highest arithmetic scores. A study of Fielder et al. [132] found that for both sexes, on physical function performances it was significantly more compared to the rest evaluated aspects by DHI questionnaire, just like in our studied population. This can be correlated with the acute complaints of the patient and the deterioration of those aspects of life. The emotional aspects were also abnormal in the population studied. This is referred to the possible harm caused by an acute episode of dizziness on the QoL, generating negative feelings, fear of completing daily tasks, shame and a sensation of incapacity and dependency, changes in social aspects of life and eventually depression. Our results are in parallel with those of Qing and Lisheng [133], who also confirmed that patients with vestibular disease present physiological distress (depression and anxiety), to emphasize the close relation between the vestibular disorder and emotional distress. In the study of Lahmann [134] it was stated that almost the half of the vertiginous population studied suffered from psychiatric and psychosocial distress. Based on the analysis of the questionnaires, it was observed that the rate of deterioration in QoL increased as the diagnosis was delayed, therefore it is essential to start the investigation as soon as possible. In addition, we assessed the various symptoms associated with dizziness, of which headache and vegetative symptoms were the most pronounced. This is of importance since a previous study showed that the appearance of headache and/or vegetative symptoms significantly negatively affects the occurrence of dizzy attacks [74].

Therefore, in order to try to avoid this remarkable alteration in the QoL, we have noticed that a proper examination of the symptoms is necessary and in our study results this was lacking. More accurately, correct diagnosis of the study population met only a 25.8%, and final diagnosis was lacking in 24.02%. In these cases, QoL did not deteriorate as much as in the rest results who had a misdiagnosis or in those with no diagnosis at all.

5.3. Different stages of Ménière's disease based on US-COMP-CCG

Our hypothesis was that with the worsening clinical parameters of MD, the values of the US-COMP-CCG parameters are worsening as well. The lateral sway in the standing test was different from the normal values, but the difference was not significant. A significant alteration of the lateral sway was expected in peripheral disorders, but only in the acute vestibular syndromes. Since we examined the patients with MD in their attack-free period, we could see only a mild difference in the standing test. Increasing of the forehead covering area showed the increasing imbalance of the patients according to the stage of MD. Imbalance and forehead covering area were not connected only to the MD, but we can see it in other vestibular dysfunctions as well. MD, as it progresses, may be manifested by less severe vertigo, with occurrences of periods of imbalance and a more prominent hearing loss. Therefore, combined examinations were done with audiometry and ENG. For stage I, the ENG was normal, for stage II, there was caloric weakness, and for stage III, there was caloric weakness and increasing attack rate, contributing to a decreased QoL [117].

The permanent damage to the balance organ, contributing to significant balance problems, was shown in the results of the US-COMP-CCG parameters. The torticollis angle parameter showed lower values in MD than in normal patients. The difference was significant. It is difficult to explain this result because all of the other parameters of the standing tests are higher in MD. If we analyze the patients' head and body movements, the decreased motivation for movement and the stiffness of the posture due to the balance disorders could explain the lower value of the torticollis angle parameter. At this point of the explanation, we must emphasize again that the examinations of US-COMP-CCG were performed in the attack-free period. During the MD attack, patients are in a very poor health condition and not suitable for these tests. The standing test results showed that the longitudinal sway and the forehead covering parameter were pathological, and the values showed increasing balance deterioration parallel to staging. Moreover, in the cases of increased forehead covering area in the stage III MD patients, a secondary visual-cortical inhibition may exist, considered based on Bergmann et al. data [135]. The torticollis angle parameter was significantly lower in every stage of MD

patients, where a possible explanation for this result is that the patients with recurrent attacks of MD move their heads less than normal patients due to constant fear of provoking a vertigo attack. Therefore, they keep their heads very straight and stiff and thus try to avoid the head movements, consequently resulting in these lower results when examined [117].

The longitudinal deviation value was substantially lower in normal vestibular patients compared to that of stage I and stage II patients, but in stage III patients are unexpectedly near normal. The differences were not of significant change. Explanation for the stage III results, could be the decreased movement efficacy of the patient due to advanced balance disorder. The longitudinal deviation was often pathological in central vestibular lesions, but MD is a true peripheral disturbance of the balance system. In the lateral sway width parameter, the value was increasing according to the stage, as we often see in clinical practice during the examination of MD patients, but the results showed no statistical significance. Angular deviation met the clinical expectations only in the stage I. By comparing the normal and all MD patient groups, the difference in the mean values showed statistical significance. These data could be explained with the fact that we examined the patients in the attack-free period. In the self spin parameter, the normal results were different from the pathological values only in the stage II patients, and the difference was statistically significant [117].

The lateral sway of the standing as well as the lateral sway width of the stepping test were pathological in every stage of MD. The lateralization in a balance disorder is not surprising nor a specific symptom, but its increasing values can help us to explain and objectivize the patients' subjective complaints. This test was furthermore combined with VOR examinations [117].

5.4. Intratympanic steroid therapy for advanced MD in correlation with the vestibular system

The current study proposes the effect of ITS on the balance system of advanced MD patients. Postural control impairment in MD may well be attributed to the endolymphatic changes and the effect of it to the labyrinth pressure which interferes

with the normal endolymphatic dynamics. Based on the detection of labyrinth impairment according to Di Girolamo and et al. [136] an abnormal static craniocorpography response was found in 70% of the patients examined. According to the results of some previously published studies, it can be concluded that the evaluation of vestibulospinal reflex is more sensitive compared to other vestibular tests [136, 137]. In a more recent study of Amer A Al Saif et al. [138], the efficiency of the sideways stepping test was investigated with the conclusion that there was a strong correlation between the stepping test and head-shaking test using video-ENG, with high specificity and sensitivity. In a previous study from our group, in which the potential use of US-COMP-CCG in the staging of MD was investigated, it was concluded that the examination of the vestibulospinal reflex using craniocorpography is a useful method in the staging of MD [118]. Based on the two studies mentioned above, we decided to use the US-COMP-CCG to examine the possible effects of ITS therapy on the balance system [118].

Steroid administration is widely used in treatment of MD, and most studies evaluate the treatment effect on the cochlear system and vertigo attacks. An improvement in symptomatic control of hearing loss and tinnitus was observed by a study of Memari et al. [85], as well as Molnár et al. [83] suggesting the beneficial nature of this treatment. Itoh and Sakata first reported on the protocol for an intratympanic injection in 1987 [84]. This treatment protocol resulted in the relief of vertigo in 80% of patients and the reduction of tinnitus in 74% [136]. Based on a systemic review, the effectiveness of the therapy varies from 32.1% to 70 % [139], vertigo control at 48.1% [140] and 60.4% [141] at one year and 59.1% [142] or 32.1% [141] at two years was detected. Although in most of the cited studies, objective vestibular tests were not used to detect the potential effects of ITS therapy. For this reason, this study focused on the objective testing after treatment. Based on the testing performance and analysis, no significant differences were found. This may be attributed to the frequency of attacks during the examination period, as well as the presence or abscense of other complaints of dizziness. Moreover, ITS treatment alleviates the vertigo spells based on the literature and therefore US-COMP-CCG was nearly always unchanged [118].

The presented study has some limitations. This was a retrospective study. First of all, MD is a fluctuating type of disorder, and a fluctuation of the symptoms could never be ruled out which is always a limitation. In the diagnosis of MD, other vestibular tests, just like the caloric test or vHIT, PTA were also used, but this study focused on the results of US-COMP-CCG, so the results of the other tests were not included [118].

5.5. Differentiation between idiopathic BPPV and secondary BPPV based on the US-COMP-CCG results

The vestibular tests are a highlight of the inner ear test, because they allow not only acute examination of the symptoms but also can be a part in the follow-up of patients. The most sensitive tool for diagnosing BPPV is the Dix-Hallpike maneuver, but in many cases, it can only be triggered in the acute phase. Because our study patients were usually examined not at the acute phase but later, according to their appointment time, the Dix-Hallpike maneuver was often negative [143]. BPPV is termed idiopathic in the most cases due to the lack of evident etiology and amounts for 50% to 70% of the cases [144]. Most common causes of s-BPPV include head trauma and vestibular neuritis, accounting for 7% to 17% and up to 15%, respectively [145, 146]. MD, migraines, and surgery of the inner ear are also known to be strongly associated with BPPV [147, 148].

As part of the neurotological examination, the US-COMP-CCG can be a tool for the most accurate examination of statokinetic tests. US-COMP-CCG provides objective and modern diagnostics, as on the basis of the registration of the test results prove damage to the vestibular system. Parameters were less pathological in i-BPPV, but pathological values were seen in s-BPPV, primarily for self-spin and forehead covering area parameters. Therefore, indicating the usefulness of US-COMP-CCG in the basis of differentiation between i-BPPV and s-BPPV [44].

5.6. The diagnosis of central vestibular disorder based on the complementary examination of the vestibulospinal reflex

In this study, we aimed to characterize the gait unsteadiness in patients suffering from central vestibular disorder and discuss the possible diagnostic usage of vestibulospinal tests in these cases. Central vestibular disorder is more likely to cause imbalance than peripheral vestibular disorder. US-COMP-CCG is a quick, non-invasive, relatively unexpensive tool suitable for the complementary diagnosis of central vestibular pathologies based on its objective measurement. Postural instability impacts everyday activities, and it has been shown that the vestibular symptoms correlate with prospective disability [149]. Patients presenting initially with vertigo and instability, attributed to subsequent cerebrovascular or cerebellar events, is higher than expected in the everyday practice [150, 151]. Based on a recent study of Gimmon et al. [152] the investigation of gait in vestibular disorders presented an impaired gait pattern in comparison to the healthy controls. In the current study, the incidence of patients with central vestibular disorder combined with gait instability was high. Patients consistently showed increased postural sway throughout both tests as compared with healthy controls. These findings supported implantation of US-COMP-CCG in gait function evaluation, and our results supported the former stating based on the schematically and analytical results that we concluded. Schniepp et al. [153] concluded in their study, that a comprehensive clinical assessment of gait performance based on a quantitative characterization of gait impairments can assist clinical decision making for the initial diagnosis and prognosis in patients, therefore strengthening the necessity of proper gait analysis. Moreover, Vanni et al. [154], by using among others the evaluation of gait and standing position on patients with vertigo and unsteadiness, they were able to reinforce the urgency to combine the examinations to raise the diagnostic accuracy.

Limitations of this study include that further vestibular evaluation would have been valuable to confirm subclinical vestibular dysfunction, whereas their correlation with postural instability remains to be explored.

5.7. Comparative study between the auditory and vestibular functions in Ménière's disease

In this study, both tests analyzed are common diagnostic methods used for the evaluation of vestibular and cochlear function adequate for the functional estimation of patients with MD and to characterise the cochleovestibular relationship in this vertiginous population. Our sample includes a representative group of MD patients, and all studies were performed at the same time presented in our tertiary care referral centre. We found that most patients were classified into a later stage of MD, the most frequent category was stage C (44.2%). According to CVT results abnormalities were detected in 67.4%, 29 of 43 patients demonstrating unilateral weakness, which is characteristic for advanced unilateral MD [119].

The possible correlation between PTA and CVT results was also investigated in previously published studies. Based on the results of Enander and Stahle [155], a retrospective study was made of 343 patients in correlation of these two tests, and it was concluded that the greater hearing loss was registered, the greater tendency to a reduction of the caloric response was detected. Their statistical analysis showed a correlation coefficient of 0.31, which is only the half part of a perfect correlation. On the other hand, in the study mentioned previously the hearing loss was determined by averaging only the lower and middle frequencies, however, a low to medium frequency hearing loss is typical only at the early stages of MD. In their study the mean duration of the disorder was defined as 8 years and most patients were found in the 40-59 dB and 60-79 dB groups, indicating later stages of MD. This finding was contrast to ours, as reduced caloric response was not correlated with the hearing loss, although in our study the hearing loss was expressed as an Extended Fletcher Index. Brix and Ehrenberger [156] stated that no clear correlation exists between hearing loss and caloric reaction. By calculating the correlation between the hearing loss and the caloric response, no significant correlations were obtained at 500, 1000 and 2000 Hz, whereas at 4000 Hz had a substantial correlation (rho = 0.85), meaning that one can expect a normal caloric response when the hearing loss is less than 40 dB at 4000 Hz. Therefore, both tests

should be performed to give a broader understanding of the status of the MD patient and for proper therapy planning [119].

Fukushima et al. [157] found that caloric weakness depends on the endolymphatic hydrops and its volume. Rey-Martinez et al. [158] supported this hypothesis, concluding that endolymphatic hydrops produces convective currents that cancel the hydrostatic effect that eventually is responsible for the CVT stimulus. The dissociation between cochlear and vestibular function could be explained by previous histopathological findings, i.e. that in the inner ear the cochlea is mostly involved by endolymphatic hydrops, followed by the saccule, utricle and the semicircular canals [159]. Pender [160] by temporal bone investigation supported this orderly lesion progression of MD, suggesting that the hydronic process staging begins in the cochlear apex, whereas the vestibular sensory cells were rarely affected [156]. Later, this fact was also strengthened by clinical investigations using MRI, and correlation was detected between hearing loss on low, medium and high frequencies and grade of hydrops, but it was not between vertigo attacks, tinnitus and CP% [161]. In our studied group, the distribution of the patients with dissociated audiometric and CVT data was the following: in 25 patients (58.2%) CP% was in the normal range, but dPTA was over 20 dB, and only in 4 patients (9.3%) reversed. This fact also highlights the previous results, i.e. that the cochlear functions are more damaged than the vestibular ones, which results in dissociation between the parameters [119].

In this study, the finding of 67.4% of abnormal caloric test is also in accordance with other studies [161, 162], indicating that CVT can be used with relatively high sensitivity in the diagnosis of MD. Nonetheless, the correlation with the audiometric results is poor. In a recent study of Limviriyakul et al. [164], it was as well concluded that weakness existed in 76.5%, concluding that the caloric test is capable to detect abnormalities of the vestibular function in all stages of MD. Therefore, both tests should be combined to evaluate the changes of function in both systems [119].

This study is limited in that it represents a retrospective review of a case series. First, the fluctuation of the complaints of the patient suffering from MD, since is a

progressive disease too must be mentioned. Second, the results of vestibular evoked myogenic potential test and electrocochleography are not included in this study [119].

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6. Conclusions

6.1. Acute vertigo episode in the Emergency department

6.1.1. Emergency department diagnosis of the vertiginous population

Proper diagnosis and information to the patient is often missing in the population visiting the ED with acute vertigo complain. Leading to increased anxiety and deterioration of the QoL, since proper guidance is missing. Therefore, a protocol to follow for this population, from treatment to guidance stand of view, may be of importance [116].

6.1.2. Assessment of the patients' quality of life visiting the Emergency department with dizziness

For the management of dizzy population self-reported measures are unique parts of the information, consequently the usage of DHI demonstrates a good reliability. According to the DHI results, patients with acute dizziness and with a clinical diagnosis of vestibular disorder indeed present with decreased QoL. Therefore, substantial investigation, an early diagnosis and the role of detailed assessment should be carried out to prevent such deterioration. For typical PVD, the neurotological examination is necessary, even for patients whose DHI score is around 16, indicating mild deterioration of QoL.

6.2. US-COMP-CCG abilities

6.2.1. Different stages of Ménière's disease based on US-COMP-CCG

The worsening results of the parameters run parallel with the progression of the disease, and this is measured objectively regardless of what the patient says about the frequency of the episodes. The deterioration of the stages is not only measured by the impairment of hearing but also with the deterioration of balance. US-COMP-CCG was capable of evaluating the severe imbalance of these patients efficiently. Alone though, it is not capable for the diagnosis of the disease [118].

6.2.2. Intratympanic steroid therapy for advanced MD in correlation with the vestibular system

Whilst ITS treatment can improve hearing impairment, as well as it decreases the vertigo attacks occurrence, it appears to have no effect on postural control. According to our results there were no changes detected on vestibular function based on US-COMP-CCG post-administration of ITS injection. Based on the literature, the effectiveness of ITS therapy is very variable, and using objective vestibular tests, no significant change was detected, so further studies are necessary to investigate the potential benefits of the therapy [118].

6.2.3. Differentiation between idiopathic and secondary BPPV based on the US-COMP-CCG results

The distinction between idiopathic and secondary cases is important. Secondary cases, unlike idiopathic cases, cannot be treated solely by repositioning maneuver (such as the Epley maneuver) but also requires treatment of the underlying disease. Based on the US-COMP-CCG result analysis, s-BPPV was detectable. US-COMP-CCG indicates late stage imbalance in MD combined with BPPV, indicates imbalance in migraine, shows uncertainty in unilateral dysfunction in vestibular neuritis and post-neuritis BPPV, whereas normal in i-BPPV [44].

6.2.4. The diagnosis of central vestibular disorder based on the complementary examination of the vestibulospinal reflex

In this study, we reinforced the recommendation to perform vestibular tests in daily clinical practice for the investigation of postural instability in patients suffering from central vestibular disorders. Clinical evaluation of imbalanced patients should include both objective measures of balance and conventional tests. Patients with imbalance were objectively registered and based on the gait analysis severe imbalance was shown. Therefore, appropriate counselling should be discussed with the patients as well as vestibular rehabilitation planning.

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6.3. Comparative study between the auditory and vestibular functions in Ménière's disease

Our study showed that audiometric changes do not directly correlate with vestibular changes, therefore no specific correlation exists between the cochlear and vestibular function loss in MD. Consequently, for therapy planning and diagnosis of the disorder both tests are necessary. Caloric test can identify the function of the affected lateral canal and audiometry indicates the severity of the existing hearing loss in MD patients [119].

7. Summary

The significance of an acute vertigo attack in daily life was under examination in this study, from both the perspective of diagnosis and management to the effect on a patient's quality of life (QoL). Questionnaires were included to investigate the efficiency of bedside examinations done in the Emergency department, and to follow-up the investigated vertiginous population. Based on these studies, in several cases, proper diagnosis and information to the patient was lacking, leading to deterioration of the QoL.

Clinical examination of the balance system was the next examined field. Balance system examination consists of the vestibuloocular and the vestibulospinal reflex (VSR). A way of recording VSR abnormalities is by ultrasound-computer-craniocorpography (US-COMP-CCG), which is the tool registration of the patient's position (Romberg test) and movement (Unterberger-Fukuda test), through its computer registration system of ultrasound signals. The results are displayed in a so-called radar scheme. The evaluation program also indicates the individual parameters for each test. Romberg test includes the longitudinal sway, lateral sway, forehead covering area, and torticollis angle parameters. Unterberger test includes the longitudinal deviation, lateral sway width, angular deviation, and self spin parameters. We investigated and verified the capability of US-COMP-CCG to monitor the severity of imbalance in different clinical stages of Ménière's disease (MD). Also, the correlation of intratympanic steroid (dexamethasone) treatment (ITS) effects among the MD and the gait system. The idiopathic and secondary benign paroxysmal positional vertigo (BPPV) were also investigated based on the hypothesis that the idiopathic BPPV does not affect the VSR, while the secondary BPPV has influence on US-COMP-CCG parameters. This analysis resulted in corroboration of secondary etiologies of BPPV. Last part of this investigation was upon the central vestibular disorder, and how these lesions are registered upon the system.

Last examined field of the research was based on the cochlear and the vestibular functions that are affected in MD. Pure tone audiometry and caloric vestibular test were used for the evaluation. According to our results, the audiometric changes did not directly correspond with the vestibular changes, therefore, no specific correlation exists between them. Therefore, for diagnosis and therapy planning both tests are necessary.

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8. Összefoglalás

Az akut szédülés mindennapi életre és az életminőségre gyakorolt hatásának vizsgálata, valamint az ágy melletti sürgősségi diagnosztika hatékonyságának elemzése érdekében kérdőíves felmérést végeztünk. Látható volt, hogy a megfelelő diagnózis és betegtájékoztatás sok esetben hiányzik, amely a beteg életminőségének romlásához vezet.

A kutatás következő részében az egyensúlyrendszer klinikai vizsgálata volt a cél, amely a vesztibulo-okuláris és a vesztibulo-spinális reflex vizsgálatából állt. Az utóbbi egyik lehetséges vizsgálati eszköze az ultrahangos számítógépes kraniokorpográfia (US-COMP-CCG). Ez két részből, az állás (Romberg teszt), valamint a helybenjárás (Unterberger-Fukuda teszt) vizsgálatából áll, az ultrahangjeleket pedig a számítógépes rendszer regisztrálja és feldolgozza. Az eredményeket ún. radar sémában jelenítjük meg, illetve láthatjuk az egyes tesztekre jellemző paramétereket. A Romberg-teszt esetén ezen értékek a longitudinal sway, lateral sway, forehead covering area és torticollis angle; az Unterberger Fukuda teszt esetén pedig a longitudinal deviation, lateral sway width, angular deviation és self spin paraméterek. A paraméterek szignifikáns különbségeket mutattak a vizsgált különböző vestibuláris léziókban szenvedőknél, valamint hasznosak az kezelések hatásának utánkövetésében is. Igazoltuk az US-COMP-CCG hasznosságát a Ménière-betegség (MD) különböző stádiumaiban megfigyelhető egyensúlyzavar súlyosságának monitorozásában. Segítségével kimutattuk, hogy az intratympanális szteroid (dexametason) nem fejt ki hatást az MD-ben szenvedő beteg egyensúlyrendszeri állapotára. A benignus paroxysmalis positionalis vertigo (BPPV) idiopátiás és szekunder típusait szintén el lehet különíteni az US-COMP-CCG segítségével, mivel az idiopátiás BPPV nem, míg a másodlagos BPPV befolyásolja az US-COMP-CCG paramétereket. Centrális vesztibuláris működészavarokban az US-COMP-CCG paraméterek szignifikánsan eltértek a kontrollcsoportban mért értékektől.

A kutatás utolsó része a cochlearis és vestibularis funkciók összevetése MD-ben, a tisztahangküszöb-audiometria és a kalorikus teszt segítségével. A két vizsgálat eredményei között nem volt korreláció, tehát az audiometriai vizsgálat során mért átlagos küszöbemelkedés nem jelenti a kalorikus teszt eredményének kóros tartományba kerülését. Következésképpen a diagnózis felállításához és a terápia tervezéséhez a két teszt együttes alkalmazása szükséges.

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10. Bibliography of candidate's publication

10.1. Publications related to the PhD thesis

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