

Acceleration and performance

Vestibular challenges in routine practice

Ph.D thesis

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Introduction

“Acceleration and Performance: Vestibular challenges in routine practice” is the title of my thesis. I think challenges of otoneurology in the 21st century are related with these concepts. With quick and efficient diagnostic methods more patients with vertigo can be managed. With application of the new diagnostic methods introduced in the last decade (video head impulse test (vHIT) and vestibular evoked myogenic potential (VEMP) test) vast improvements have been made to achieve these goals.

Background of basic research

Physiologic function of the vestibulo-ocular reflex (VOR) is ensure clear vision during fast head movements by to stabilizing the image of environmental focused objects in the fovea of the retina. During the reflex the eyes are rotating with the same speed, but into the opposite direction to the head motion. Impairment of vestibular function in the low and/or high frequency range may decrease the performance of the VOR. Vestibular reaction evoked by low frequency range stimulation can be examined with the caloric test; vestibular reaction evoked by high frequency stimulation can be examined with the head impulse test. In everyday life quick head movements representing high frequency stimulation are common, therefore the head impulse test is of immense importance.

After unilateral acute vestibular lesion the function of the VOR in response to high frequency stimuli recover only in approximately 50% of the cases. In one-third of the patients the lack of recovery of the reflex associates with chronic dizziness. Recovery of the VOR is mainly supported by the rehabilitation of the non-linear vestibular afferent pathways.

Background of Clinical Research

First examination of patients with acute vertigo is in the Emergency Ward (EW) in 25% of the cases. In the EW in cases of acute isolated vertigo ongoing since hours or days the most important task is to differentiate between the posterior scale strokes carrying the risk of permanent health damage and the benign vestibular neuritis. According to contemporary international data approximately 35% of stroke cases and 90% of TIA cases associated with isolated dizziness are largely misdiagnosed in the EW. Due to misdiagnosis the chance of early secondary prevention of a repeated stroke may be lost, and in case of ineffective monitoring the progression of the symptoms may result in death .

Objectives

The thesis includes three main objectives: *basic research* of the linear and non-linear pathways of VOR, *clinical research* of the emergency management of acute vertigo, and *research of the history*

of medicine by processing the publications of Hungarian researchers achieving great progress in the field of the otoneurology.

In *basic research* the thesis seeks answer to the following questions:

1. Is it possible to stimulate simultaneously the semicircular canals with high frequency and low frequency stimuli, and can high frequency, rapid acceleration signal (head impulse) be influenced by low frequency stimulation (caloric)?
2. Does an acute vestibular asymmetry diminish the vergence-mediated gain increase?

The objective of the *clinical research* was to investigate in a prospective study the efficiency of a new bedside test called H.I.N.T.S. Plus including oculomotor analysis and assessment of hearing in the diagnosis of patients with acute vestibular syndrome (AVS). H.I.N.T.S. Plus is a mosaic word, which refers to the abbreviation of the following tests: Head Impulse, Nystagmus, Test of Skew. Lastly, "plus" refers to the examination of hearing.

Clinical research investigated the following issues:

1. Among patients diagnosed with AVS in the EW of Győr what is the ratio between central and peripheral vestibular origin assessed with bedside and with instrumental H.I.N.T.S. Plus test?
2. Does the instrumental H.I.N.T.S. Plus test applied in the EW of Győr in cases with AVS improve the diagnostic efficiency?

3. What is the percentage of the positive native skull CT examinations performed to exclude posterior scale stroke in the EW of Győr? Is the acute native skull CT examination helpful in the diagnosis of dizziness in the EW of Győr?
4. What is the percentage of the posterior scale strokes presenting with isolated dizziness without neurologic signs except nystagmus in the EW of Győr?
5. What is the percentage of the false positive instrumental H.I.N.T.S. Plus examinations in the EW of Győr?
6. Among patients with AVS what is the percentage of the acute unilateral cochleovestibular symptoms diagnosed by the instrumental H.I.N.T.S. Plus test?

In my research of the history of medicine, I investigated the experimental methods and conclusions of Hőgyes in association with VOR, Bárány's research on the caloric test and Halmagyi's work on the head impulse test.

Methods

The function of the linear and non-linear afferent pathways was examined by the combination of the two basic vestibular tests, the caloric and head impulse test.

To answer the first two questions of basic research, the following experiment was done:

Caloric warm (44°C) and cold (24, 27 & 30°C) water irrigations of the left ear were performed in seven healthy human subjects (4 men,

3 women, mean age, 37 years, ranging from 19 to 51 years of age) with the lateral semicircular canals oriented approximately earth vertical and approximately earth horizontal. Prior to caloric irrigation, baseline video head impulse testing (vHIT) was obtained in the plane of the lateral semicircular canals. Video HIT was carried out with the ICS Impulse® video goggles (GN Otometrics, Taastrup, Denmark). Following the irrigation, five high acceleration head impulses to the left and to the right were administered over a time interval lasting 30 seconds, and in random order. This block of two times five impulses (both left and right) was repeated five times over 150 seconds, resulting in five blocks. Following caloric irrigation with the lateral canal in the vertical position, the experiment was repeated in its entirety, including caloric irrigation with the lateral canal in the horizontal position. Statistical analysis was carried out using Graphpad Software. Average gain values measured at different times following irrigation were compared using nonparametric, one-way analysis of variance (Friedman test and Dunn's multiple comparison post-test).

To answer the third question of basic research, the following experiment was done:

Nine healthy individuals (4 women, 5 men, average age, 32 years old; minimum, 18 years old; maximum, 51years old), with no history of otologic or cochleovestibular disorders were recruited. Video HIT (vHIT) was carried out in the plane of the lateral semicircular canal

(SCC). Baseline HIT testing and caloric stimulation were achieved using a standard calibration including the lateral SCCs in an earth-vertical position. Subjects were tested in with an eye-level target, positioned directly straight ahead at a distance of 120 cm, and precisely in each patient's forefront (far distance viewing) and 15 cm (near sighted viewing). Caloric irrigation lasted 40 seconds and was carried out in the right ear in all subjects at a temperature of 24°C. As a baseline measurement, and following irrigation, 6-8 high-acceleration head impulses to the right and to the left (peak head velocity >120°/s) were administered in an alternating manner, over a time interval of 30 seconds. Following three to four impulses to the right and left, the viewing distance was altered from near sighted viewing to far distance viewing.

The raw data of head and eye velocity traces were exported into a Matlab-file (The MathWorks, Natick, MA). Data groups were compared using a non-parametric ANOVA (we did not assume Gaussian distributions), the Friedman's test and Dunn's post-tests.

To answer the questions of clinical research the following experiment was done:

From 1st of March, 2016 to 1st of March, 2017 125 patients (62 women, 63 men, average age, 53 years old) with acute vertigo presented in the EW of the Petz Aladár County Teaching Hospital were examined with bedside and instrumental H.I.N.T.S. Plus test For the instrumental H.I.N.T.S. Plus test the ICS Impulse® video

goggles (GN Otometrics, Taastrup, Denmark) and pure tone audiometry (Interacustics A/S DK 5610Assens, version DA931) was used.

The diagnostic criteria for AVS included acute dizziness, accompanied by nausea, vomitus, gait unsteadiness, nystagmus and the intolerance to head motion lasting more than 24 hours. Isolated AVS was diagnosed in the absence neurological signs except nystagmus. In patients diagnosed with central AVS brain MRI and MRA, and/or neck vessel Duplex Ultrasound examination was performed.

Results

Results of the first experiment of basic research include the following:

- Cold-water irrigation (24°C) significantly ($p < 0.001$) decreased the rVOR gain of ipsilateral head-impulse tests.
- The rVOR gain of contralateral (i.e., rightward) head impulses, however, was not significantly influenced by cold-water irrigation.
- Likewise, rVOR gains of head-impulse tests to either side were not affected by ipsilateral warm-water (44°C) caloric stimulation.
- Control experiments with head-impulse tests applied to both sides following warm- and cold-water caloric stimulation with

the plane of lateral SCC-oriented earth horizontal (the subject's head inclined 30° from a supine position) did not reveal changes of rVOR gains when compared to baseline.

Results of the second experiment of basic research include the following:

- Highly significant difference between far distance viewing and near sighted viewing in both directions. The gain increased in average 27.7 % for impulses to the right during convergence.
- A highly significant difference was noted between the baseline and caloric during far distance viewing for impulses to the right (caloric decreased the aVOR gain from unity gain to 0.67 in average), but no difference for impulses to the left.
- A highly significant difference between impulses during far distance viewing and near sighted viewing (vergence) following caloric irrigation with impulses to the right (in average 22 % increase when near sighted viewing) and significant difference between far distance viewing and near sighted viewing during impulses to the left.
- There was no significant difference between gain increase (gain change) due to vergence during impulses to the right prior and following caloric irrigation, change in average (\pm SD) during baseline measurement: 27.7 % (\pm 13,2) and following caloric irrigation: 22,2 % (\pm 18.2).

Results of clinical research include the following:

- In patients with AVS H.I.N.T.S. Plus test revealed peripheral origin in 58% and central origin 42% of the cases in the EW of Győr. Instrumental H.I.N.T.S. Plus test altered the ratio in peripheral cases to 69% and in the central cases decreased to 31%.
- The acute cranial computed tomography examination identified ischemic vertebro-basilar stroke only in 4.8% of the cases.
- In 26.4% of central cases identified by the non-instrumental H.I.N.T.S. Plus test the instrumental H.I.N.T.S. Plus revealed to peripheral origin, largely due to cases with inferior neuritis and/or superior or total neuritis with covert saccades in the EW of Győr.
- Isolated vertigo without additional focal neurologic signs was found in 61.5% of the cases with posterior circulation stroke identified by instrumental H.I.N.T.S. Plus test in the EW of Győr.
- In the EW of Győr in 15.7 % of stroke cases the instrumental H.I.N.T.S. Plus test was proven falsely positive due to verified benign dizziness identified during follow-up examinations.
- Instrumental H.I.N.T.S. Plus tests, in 9 %, diagnosed acute unilateral cochleovestibular lesions, but and was not capable to identify of the etiology of AVS in the EW of Győr.

Results of historical research include the following:

Although several data can be found about vertigo in literature and historical sources only the work of researchers in the 19th century including Flourens, Ménière, Breuer, and others revealed that dizziness can also be attributed to inner ear dysfunction. The discovery of the vestibulo-ocular reflex was an important milestone (Endre Hógyes, 1884). The milestone discovery of Hógyes, accomplished by stimulating individual labyrinth receptors and recording the activity of eye muscles was verified by János Szentágothai in 1952. Low-frequency lesions of the angular vestibulo-ocular reflex can be detected by caloric test (Robert Bárány, 1906), and the high-frequency lesions by the head impulse test (Gabor Michael Halmagyi and Ian Stewart Curthoys, 1988). In the past decade new, non-invasive test methods (video head impulse test and vestibular evoked myogenic potential) have been introduced for the independent, precise examination of all vestibular end-organs.

Conclusions

The conclusions of the basic research:

1. Vestibular end-organs can be stimulated by both high frequency and low frequency stimuli simultaneously, and the high frequency fast acceleration signal (head impulse) can be influenced by low frequency stimulation (caloric). We concluded that the combination of the two basic vestibular tests

(caloric and head impulse) can effectively model the pathologic head impulse test by cold caloric irrigation.

2. The results of the second experiment showed that an acute vestibular asymmetry does not abolish the vergence-mediated rVOR gain increase among healthy human individuals through the use of low frequency cold water stimulation. We concluded therefore, that cold water caloric stimulation does not influence the functioning of non-linear/phasic vestibular afferent pathways. In spite of the low frequency vestibular inhibition the gain value of rVOR can be increased in vergence; this shows the importance of optokinetic training in vestibular rehabilitation.

Conclusions of the clinical research:

1. Native skull CT examinations were frequently ordered in peripheral vestibular neuritis.
2. More than 25% of skull CT examinations made in the EW of Győr did not diagnose a posterior scale stroke, and nearly two thirds of stroke cases manifested themselves by isolated vertigo without additional focal neurologic signs. The false negative CT result and the absence of neurologic signs can be misleading.
3. Notably, both bedside and instrumental H.I.N.T.S Plus examinations by excluding the potentially life-threatening central cases increased the diagnostic accuracy and patient's safety.

4. Strikingly, the efficiency may be increased by the operational use of the instrumental H.I.N.T.S. Plus method.
5. Reportedly, there were falsely positive stroke cases diagnosed as posterior scale strokes, performed by the instrumental H.I.N.T.S. Plus examination method, however, it is worth emphasizing, the false positive result did not endanger the safety of the patients.
6. In the case of acute isolated unilateral cochleovestibular lesions, neither an instrumental H.I.N.T.S. Plus, nor a MRI examination could verify the exact etiology of the AVS. Patient safety measures can be increased if and when these cases are considered inner ear ischemia and the patients are examined on this basis.

Conclusion of historical research:

The findings of Hőgyes, Bárány and Halmágyi are milestones in the development of otoneurology, because these findings make possible the detection of VOR lesions both to low and high frequency stimulations, and the examination of the VOR has significant practical consequences in the vestibular diagnostics.

Personal Publications

Personal publications associated to the thesis:

1. Tamás TL, Tompos T, Garai T, Szirmai Á. (2015) New test methods in otoneurology Otorhinolaryngologia Hungarica, 61: 49-53.
2. Tamás TL, Tompos T, Garai T, Szirmai Á. (2015) Objective tests of end-organs of the inner ear: our experiments. Otorhinolaryngologia Hungarica, 61: 54-58.
3. Tamás TL, Weber KP, Bockisch CJ, Straumann D, Lasker DM, Büki B, Tarnutzer AA, (2016) Cold Thermal Irrigation Decreases the Ipsilateral Gain of the Vestibulo-Ocular Reflex. Ear Hear, 38: 193-199.
IF: 3,120
4. Tamás TL, Garai T, Tompos T, Szirmai Á. (2016) Vertigo in the Emergency Department: new bedside tests. Orv Hetil, 157: 403-409.
5. Tamás TL, Mike A. (2017): Emergency diagnosis of posterior scale strokes with isolated vertigo. Magyar Mentésügy, 31: 23-29.
6. Tamás TL, Garai T, Király I, Mike A, Nagy Cs, Paukovics Á, Schmidt P, Szatmári F, Tompos T, Vadvári Á, Szirmai Á. (2017) Emergency diagnosis of the acute vestibular syndrome Orv Hetil, 158: 2029-2040.
IF: 0,322

7. Tamás TL, Lundberg YW, Büki B. (2018) Vergence increases the gain of the human angular vestibulo-ocular reflex during peripheral hyposensitivity elicited by cold thermal irrigation. *J Vestib Res*, 27: 265-270.

IF:2,865

Publications independent from the essay:

1. Tamás TL, Pellek S, Zemplén B. (2001) Paratracheal and upper mediastinal dissections in radical cases of glotto-subglottic tumors: our experience. *Otorhinolaryngologia Hungarica*, 47: 32-36.

Cummulative IF: 6,307