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OTOLOGY

Horizontal VOR function shows frequency dynamics in vestibular schwannoma

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Abstract The objective of this retrospective study was to investigate the horizontal vestibulo-ocular reflex (hVOR) pathway with caloric test (low-frequency hVOR) and video head impulse test (vHIT) (high-frequency hVOR) in patients with sporadic vestibular schwannoma (69 patients, 27–86 years, mean age 58.1 years) and to compare both test methods in terms of their sensitivity and specificity to detect a retrocochlear lesion. Test results with a unilateral weakness ($UW_{Caloric}$) >25 % (caloric test) or a Mean-Gain-$_{vHIT}$ <0.79/asymmetry ratio of Gain (AR-Gain$_{vHIT}$) >8.5 % and accompanied refixation saccades (vHIT) were considered abnormal. The overall sensitivity of the caloric test was 72 %. The evaluation of AR-Gain$_{vHIT}$ detected more abnormal cases than did Mean-Gain$_{vHIT}$ (44 vs. 36 %). In up to 4 %, a normal caloric test result was related to an abnormal vHIT. There was only a moderate correlation of $UW_{Caloric}$ and AR-Gain$_{vHIT}$ ($r = 0.54$, $p < 0.05$) with a linear regression line intercept/slope of 32.2/0.9 ($p < 0.05$). Receiver operating characteristics curve analysis exhibited at a $UW_{Caloric}$ of 50 % a vHIT sensitivity/specificity/positive predictive value/negative predictive value of 0.45/0.9/0.94/0.42. Vestibular testing at varying frequencies provides deeper insights into hVOR function and is helpful in detecting a cerebello-pontine lesion. Whereas caloric test yields a high sensitivity for nerve dysfunction, vHIT test reveals a remaining function of hVOR in the high-frequency range.

Introduction

Caloric testing and the recently introduced video head impulse test (vHIT) are reliable test methods to evaluate the function of the lateral semicircular canal and superior vestibular nerve, i.e., horizontal vestibulo-ocular reflex (hVOR). HVOR function is essential in daily life to generate visual stabilization during horizontal head movements and walking. Vestibular schwannoma (VS) is a common tumor in the cerebello-pontine angle; since VS originates from the vestibular nerve, it can cause vertigo symptoms by deterioration of hVOR function.

Caloric testing has been the standard examination method for hVOR in unilateral or bilateral vestibular dysfunction for over 100 years. The disadvantages of caloric testing consist in its time-consuming test procedure and its discomfort for patients due to induced vertigo and nausea. Besides this, the thermal stimulus is non-physiologic and the response has a high inter-individual variety with ≤25 % of normal values.

The video head impulse test (vHIT) is a new VOR test method, which is safe, easy to perform and comparable to scleral search-coil measurements [1–3]. It is indicative for a VOR function loss when eye/head velocity gain is low, i.e., compensatory eye movement does not equal head rotation to brief high-acceleration head impulses and is therefore accompanied by corrective catch-up saccades to keep the gaze straight ahead.

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Surprisingly, testing hVOR function with caloric test and vHIT can yield conflicting results, e.g., the caloric test indicates a vestibular hypofunction but the vHIT does not. This has been proven in few studies, especially for peripheral vestibular disorders such as Menière's disease (MD) [4, 5] and vestibular neuritis (VN) [6–8], but not for retrocochlear lesions such as VS in a higher number of patients [9].

Therefore, the aim of this study was to evaluate the diagnostic value of caloric test and vHIT in patients with sporadic unilateral VS, i.e., to investigate whether both tests are sensitive and specific to detect a VS-related hVOR function deficit. Furthermore, vHIT test results were examined in relation to the caloric test and the amount of caloric unilateral weakness ($UW_{Caloric}$) matching the highest sensitivity and specificity of the vHIT is defined. Since the response of the horizontal semicircular canal to caloric irrigation is equivalent to low-frequency rotatory stimulation (0.002–0.004 Hz) [10] and vHIT tests hVOR in a high-frequency range (5–7 Hz) [2], the results will be discussed in terms of their implications for vestibular frequency dynamics of hVOR function in vestibular schwannoma.

Materials and methods

Subjects

This is a retrospective study of patients with untreated sporadic unilateral VS, based on 1.5 T cranial MRI scanning (Magnetom Avanto, Siemens, Germany; 1 mm axial T2 space and contrast enhanced T1 vibe) in a tertiary referral center. VS was assessed according to the Hanover classification [11]. All patients underwent a detailed clinical history, a standard clinical ENT/neurological examination and vestibular testing (caloric test and vHIT) on the same day. The exclusion criteria were: patients with acute vestibular failure within the 2 weeks immediately preceding the vestibular testing, after microsurgery or radiotherapy for VS or previous mastoid surgery, concomitant diseases influencing the vestibular system, neurofibromatosis type 1/type 2 or the intake of vigilance-affecting drugs. The study subjects comprised 69 patients (39 females and 30 males; mean age 58.1 years; range 27–86 years). In 37 subjects (54 %) the VS was situated on the left side and in 32 (46 %) on the right side. This study was approved by the local ethic committee.

Caloric tests

The caloric tests were performed in a supine position with a 30-degree head elevation with water (30/44 °C, 75 ml, irrigation time 30 s, inter-irrigational interval >7 min). Horizontal eye movements were recorded with a binocular video oculography system (VN 415™, Interacoustics, Denmark). The maximum velocity of the slow phase component of spontaneous nystagmus and bithermal-induced nystagmus during a 30-s culmination phase was analyzed for unilateral weakness ($UW_{Caloric}$) as determined by Jongkees formula. A pathological $UW_{Caloric}$ was present at >25 % according to normative data in our laboratory. Subjects with a spontaneous nystagmus >4° of slow phase velocity were rejected from the study [12].

Video head impulse testing

The EyeSeeCam™ system was used to record hVOR with vHIT. Subjects were instructed to fixate a dot located on a wall 1.2 m straight ahead. A minimum of 10 head impulses in the horizontal plane (yaw-axis rotation amplitude 15°–20°, duration 150–200 ms, peak velocity 200°/s) were randomly performed manually to both sides, with unpredictable timing and direction. The velocities of eye and head [°/s] were captured at 40, 60 and 80 ms after the head impulse was initiated and were averaged for both. The velocity gain of the hVOR ($Mean\text{-}Gain_{vHIT}$) is represented by the ratio of mean eye velocity [°/s] over mean head velocity [°/s]. Gain asymmetry ratio ($AR\text{-}Gain_{vHIT}$) is defined by the following equation:

Asymmetry ratio

$$= \frac{\text{Gain unaffected side - Gain affected side}}{\text{Gain unaffected side + Gain affected side}} \times 100\ \%$$

Refixation saccades were sampled within 700 ms after the onset of head impulses and with amplitudes up to 400°/s eye velocity. The vHIT results were classified as abnormal if two conditions were met: abnormal values for either $Mean\text{-}gain_{vHIT}$ or $AR\text{-}Gain_{vHIT}$ and the presence of refixation saccades. Refixation saccades were classified as covert if they occurred before the end of the head impulse and as overt afterwards. Normal hVOR $Mean\text{-}gain_{vHIT}$ and $AR\text{-}Gain_{vHIT}$ are 0.99 ± 0.1 and 3.5 ± 2.5, respectively. For the cut-off value, we defined an abnormal $Mean\text{-}gain_{vHIT}$ (<0.79) and $AR\text{-}Gain_{vHIT}$ (>8.5 %) as the outside of mean $\pm$ 2 SD found in 30 normal subjects in our laboratory.

Data analysis

The data of all patients were numerically captured, continuous variables were expressed as mean (SD), and categorical variables were expressed as frequencies and percentages. The significance of any differences between groups was evaluated by the t-test for dependent samples ($p < 0.05$). Linear regression was used to determine the significance of the correlation between the $UW_{Caloric}$ and the $AR\text{-}Gain_{vHIT}$. An analysis of variance (ANOVA) was carried out to assess the influence of predictor variables (sex, age, tumor grade).

ROC curve was plotted [sensitivity vs. (1−specificity)] to compare the results of $UW_{Caloric}$ and Mean-Gain$_{vHIT}$/AR-Gain$_{vHIT}$. Statistical analyses were performed using SPSS for Windows 20.0.0.

Results

Evaluation of hVOR in different tumor grades

Abnormal results for Mean-Gain$_{vHIT}$, AR-Gain$_{vHIT}$ and $UW_{Caloric}$ were found in 25 (36 %), 30 (44 %) and 50 subjects (72 %), respectively. This corresponds to a test sensitivity of 36–44 % for vHIT and 72 % for caloric test. The side with abnormal caloric test and vHIT values was always in agreement with the side identified as having VS based on MRI scanning.

There was no significant influence of sex or age on tumor grade, caloric or vHIT test results. There were significantly fewer subjects affected at a lower VS tumor grade (T1/T2) in caloric testing compared with subjects at higher VS tumor grades (T3/T4), whereas this dependence on tumor grade was not detected in vHIT testing. AR-Gain$_{vHIT}$ revealed an abnormal result in 5/69 subjects (7 %) whereas Mean-Gain$_{vHIT}$ detected them as normal. Demographics and details are provided in Table 1. In Table 2, the mean values of $UW_{Caloric}$, Mean-Gain$_{vHIT}$ and AR-Gain$_{vHIT}$ are summarized for each tumor grade. Subjects with lower tumor grades exhibited a significant lower $UW_{Caloric}$ compared with higher tumor grades whereas Mean-Gain$_{vHIT}$ and AR-Gain$_{vHIT}$ values were not significantly different.

Comparison of caloric test and vHIT

There was a significant but modest linear correlation between $UW_{Caloric}$ and AR-Gain$_{vHIT}$ values ($r = 0.54$, $p < 0.05$) in VS patients (Fig. 1). The intercept of the linear regression line was 32.2. The slope of the line (0.9; $p < 0.05$) indicates that VS patients have slightly larger asymmetries in their response to vHIT than to caloric. The linear correlation of $UW_{Caloric}$ and Gain$_{vHIT}$ ($r = 0.48$, $p < 0.05$) was slightly lower than that of the former. Table 3 provides the results of the caloric test and vHIT. An abnormal vHIT result related to a normal caloric test was seen for Mean-Gain$_{vHIT}$ in two cases (3 %) and for AR-Gain$_{vHIT}$ in 4 cases (6 %), respectively. This was not dependent on tumor grade. A normal vHIT accompanied by a normal caloric test result was found in 17 cases (25 %) for Mean-Gain$_{vHIT}$ and in 15 cases (22 %) for AR-Gain$_{vHIT}$, respectively. In two cases (8 %), there was a reduction of the contralateral gain to abnormal values without occurrence of refixation saccades. This was correlated to a gain reduction <0.25 on the VS side and a $UW_{Caloric}$ >90 %.
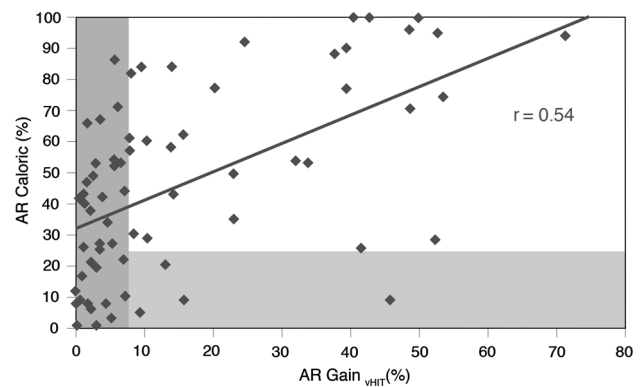

Fig. 1 Linear regression of unilateral caloric weakness ($UW_{Caloric}$) as a function of vHIT gain-asymmetry (AR-Gain$_{vHIT}$)

Table 1 Tumor grades and abnormal test results (n/ %) within the entire sample population of unilateral vestibular schwannoma

Grade	N	Age	Abnormal results n (%)		
			$UW_{Caloric}$	Mean-Gain$_{vHIT}$	AR-Gain$_{vHIT}$
T1	29	57 ± 12	18 (62 %)	7 (24 %)	9 (31 %)
T2	11	61 ± 18	7 (64 %)	5 (45 %)	6 (55 %)
T3	16	59 ± 13	13 (81 %)	5 (31 %)	8 (50 %)
T4	13	57 ± 18	12 (92 %)	8 (62 %)	7 (54 %)
	69	58 ± 14	50 (72 %)	25 (36 %)	30 (43 %)

Table 2 Unilateral weakness ($UW_{Caloric}$) in caloric test and gain/ gain asymmetry (Mean-Gain$_{vHIT}$/AR-Gain$_{vHIT}$) in vHIT for all tumor grades

Grade	N	$UW_{Caloric}$	Mean-Gain$_{vHIT}$	AR-Gain$_{vHIT}$
T1	29	38 ± 27	0.87 ± 0.25	11 ± 15
T2	11	39 ± 35	0.73 ± 0.31	20 ± 20
T3	16	51 ± 26	0.81 ± 0.27	16 ± 17
T4	13	68 ± 27	0.66 ± 0.29	22 ± 22
N = 69	69	47 ± 30	0.80 ± 0.28	15 ± 18

Table 3 Distribution of normal and abnormal caloric test results related to vHIT results

Caloric test, UW (%)	Video head impulse test			
	Normal n (%)		Abnormal n (%)	
	Mean-Gain$_{vHIT}$	AR-Gain$_{vHIT}$	Mean-Gain$_{vHIT}$	AR-Gain$_{vHIT}$
≤25	17 (25 %)	15 (22 %)	2 (3 %)	4 (6 %)
>25	27 (39 %)	24 (35 %)	23 (33 %)	26 (38 %)

Table 4 Results of descriptive statistical analysis for different cut-off points in vHIT gain/gain-asymmetry

	Cut-off	Sensitivity	Specificity	Prevalence	Pos. PV	Neg. PV	Efficacy
AR-Gain$_{vHIT}$	8	0.45	0.94	0.34	0.94	0.42	0.60
	10	0.38	1	0.27	1	0.41	0.57
	12	0.36	1	0.25	1	0.40	0.55
Mean-Gain$_{vHIT}$	0.7	0.29	1	0.20	1	0.37	0.5
	0.79	0.36	1	0.25	1	0.40	0.55
	0.9	0.55	0.9	0.41	0.93	0.46	0.65
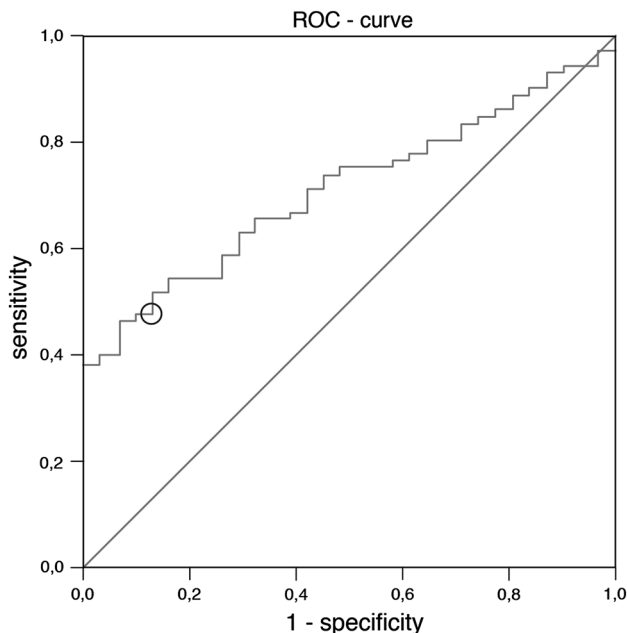
Fig. 2 Receiver-operating characteristic (ROC) curve for unilateral weakness in caloric test versus gain-asymmetry in vHIT. The best cut-off point is 50 %

To enhance test sensitivity for vHIT with reliable specificity, the best cut-off values for Mean-Gain$_{vHIT}$ and AR-Gain$_{vHIT}$ were calculated from ROC curve analysis and are shown in Table 4. Considering the results of caloric irrigation as the independent variable, the ROC curve, predicting an optimal dichotomous outcome of vHIT (normal or abnormal), is shown in Fig. 2. A cut-off point of 50 % UW$_{Caloric}$ was associated with a vHIT test sensitivity of 0.45 and a specificity of 0.9. The area under the curve was calculated at 0.713 (95 % CI = 0.617/0.810). The positive predictive value of the vHIT was 0.94 and the negative predictive value was 0.42. Subjects with a UW$_{Caloric}$ <50 % exhibited a Mean-Gain$_{vHIT}$ and AR-Gain$_{vHIT}$ of 0.89 ± 0.23 and 9 ± 13, which were significantly higher ($p < 0.05$) than in subjects with a UW$_{Calorc}$ ≥50 % exhibiting a Mean-Gain$_{vHIT}$ and AR-Gain$_{vHIT}$ of 0.67 ± 0.29 and 24 ± 20, respectively.

Discussion

Head impulse test and caloric test are both primarily tests of peripheral vestibular function. They have been shown to detect a hVOR deficit since they can be abnormal in vestibular neuritis, Menière`s disease, after intratympanic gentamicin therapy, vestibular nerve deafferentation and even in isolated vestibular nuclear infarction but seldom in vertebrobasilar stroke [4, 5, 7, 8, 15, 24, 29, 30]. Therefore, a retrocochlear lesion like VS can cause a hVOR deficit, which should be detectable with vHIT and caloric test, since VS can either deteriorate peripheral hVOR function due to vestibular nerve compression or diminished blood supply of the inner ear [23].

The results of our study show that caloric testing and vHIT differentiate significantly between the affected and unaffected side of VS according to MRI. However, for the detection of a hVOR deficit, test sensitivities of caloric and vHIT differ, i.e., caloric irrigation reveals an abnormal hVOR function statistically more often than vHIT. Since caloric testing reflects low-frequency hVOR changes and vHIT is able to show high-frequency hVOR deficiencies, the combination of both tests permits the interpretation of hVOR impairment in a frequency-dependent manner. From the results of our study it can be concluded that in VS the whole frequency range of hVOR function can deteriorate, however, the results also clearly show that the low-frequency range is more often affected, whereas the high-frequency range is preserved. To identify both the low- and high-frequency hVOR range, caloric test and vHIT are necessary.

During head motion, vestibular signals have to be encoded in a wide frequency range from static head position to high-acceleration head turns. A frequency-dependent organization of hVOR can be attributed to distinct functional subgroups of vestibular hair cells with different intrinsic properties and response dynamics at each synaptic level. It has been shown, that the sensory–motor transformation occurs in parallel frequency-tuned pathways [31]. In fact, regular vestibular afferents that terminate onto type II hair cells have a low velocity detection threshold and transmit more information about low-frequency head

rotations (<4 Hz). In contrast, irregular vestibular afferents which terminate onto type I hair cells make their primary contribution to VOR processing for high-frequency head rotations [32].

Evidence of a frequency-dependent impairment of hVOR function in various peripheral vestibulopathies such as Menière`s disease and vestibular neuritis derives from earlier studies. Perez and Rama-Lopez [13] found the clinical HIT to be a low sensitive but highly specific test when compared with the caloric test. In patients with chronic vestibular neuritis (VN), Mahringer and Rambold [7] have recently demonstrated that a caloric test asymmetry of >25 % was associated with a pathologic vHIT in only 33 %, whereas Schmidt-Priscoveanu et al. [14] found that high-frequency VOR did not recover in a follow-up of VN [7, 13, 14]. The latter is in line with former studies, which have shown that the VOR remains deficient in response to high-frequency, high-acceleration or high-velocity rotations [15–17].

In general, the results of our study and literature data show that in the case of VS and other peripheral vestibulopathies both low (caloric) and high- (vHIT) frequency tests are necessary to reflect the whole hVOR frequency spectrum in case of impairment. The clinical relevance of the caloric test and vHIT is supported by the finding that in only few VS cases a normal caloric test was accompanied by an abnormal vHIT.

Tringali et al. [18] observed a good correlation of caloric weakness and tumor grade in a series of 629 patients. The frequency-dependent diagnostic of VS in our study reveals that there is only a tumor grade dependent influence on caloric test results but not on vHIT results. This can be interpreted as a result of a different susceptibility of regular and irregular vestibular nerve fibers due to tumor pressure, since in semicircular canals regular afferents have smaller axon diameter [19]. Furthermore, it has been shown that even the vertical canals can contribute to hVOR answer thus influencing the caloric test result [20], but in contrast there has been no evidence of vertical canal contribution to hVOR answer in vHIT until now. Since VS is a slow growing tumor, vestibular impairment is a chronic process accompanied by central vestibular compensation. For high-frequency hVOR, there may be proposed a higher ability to recover, which has been demonstrated in a vestibular neuritis follow-up study with vHIT and caloric test [8]. Furthermore, it has been shown that different parts of vestibulocerebellum (e.g., nodulus/uvula) are attributed to a different modulation of the slow component hVOR (velocity storage) and VOR gain [21, 22].

In our study, linear regression analysis reveals only a moderate correlation of caloric and vHIT test results. Comparable data have been shown in Menière's disease (MD) before and after gentamicin treatment using $UW_{Caloric}$ and

search-coil head thrust test or in VS with motorized head impulse test [4, 5, 23]. The intercepts/slopes of the linear regression equation fitting $UW_{Caloric}$ as a function of AR-$Gain_{vHIT}$ of our study is in between that for MD as well as chronic VN and acute VN (54.7/0.26) and near to mixed acute plus chronic VN in former studies (caloric/search-coil measurements) [4, 14]. Therefore, disparity of caloric and vHIT test seems to be dependent more on whether the disease is acute or chronic than on a specific etiology in peripheral vestibular pathologies.

For assessment of high-frequency hVOR recent studies have used besides the occurrence of refixation saccades (overt/covert) either ipsilesional gain or gain asymmetry for quantification of vHIT results. Using the vHIT in different peripheral vestibulopathies it has been demonstrated that both the ipsi- and contralesional gain can be reduced and in rare cases ipsilesional hVOR gain reduction can even occur without refixation saccades [24]. In this study, we therefore compared ipsilesional gain (Mean-$Gain_{vHIT}$) and gain asymmetry ratio (AR-$Gain_{vHIT}$). Combined use of AR-$Gain_{vHIT}$ and saccades revealed more abnormal cases in vHIT and provides a better correlation with respect to the $UW_{Caloric}$ than Mean-$Gain_{vHIT}$. But since correlation of $UW_{Caloric}$ and AR-$Gain_{vHIT}$ or Mean-Gan_{vHIT} in VS patients is significant but only moderate, it cannot conclusively predict that an abnormal caloric test is always associated with an abnormality in vHIT. In ROC analysis, we determined the optimal degree of $UW_{Caloric}$ to separate between normal and abnormal if vHIT test is used to discriminate between these. Our discriminant $UW_{Caloric}$ in VS is close to those which have been reported using caloric and bedside HIT or vHIT in other peripheral vestibulopathies [8, 13]. Therefore, vHIT is more sensitive in the presence of a severe canal paresis [25–27].

Using either Mean-$Gain_{vHIT}$ or AR-$Gain_{vHIT}$, we determined vHIT sensitivity and specificity as well as positive and negative predictive test values. Liu et al. [28] found the sensitivity, specificity, positive and negative predictive value of HIT to be of 54.9, 90.6, 86.7, and 64.4 %, respectively, if the results of caloric test were considered as the standard method to evaluate the hVOR. In our study, considering the MRI as standard method to detect a VS, these results could only be reached by changing the cut-off values for Mean-$Gain_{vHIT}$ to >0.9 and AR-$Gain_{vHIT}$ to <8.

Conclusion

For detection of hVOR impairment within a broad frequency spectrum, both caloric testing and vHIT are necessary in VS. Our findings suggest substantial preservation of high-acceleration canal function. This has to be considered in surgical interventions or radiotherapy for VS, since then

they can still cause vertigo symptoms. VS tumor grade has an influence on caloric test results but not on vHIT. AR-Gain$_{vHIT}$ should be used in assessment of hVOR function. A frequency dynamic analysis of hVOR function is recommended in acute or chronic peripheral vestibulopathies.

Conflict of interest The authors declare no financial interest.

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