AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY FOUNDATION

Original Research—Otology & Neurotology

Otolaryngology–Head and Neck Surgery
2023, Vol. 169(5) 1268–1275

DOI: 10.1002/ohn.399
http://otojournal.org
WILEY

Vestibular Tests Related to Tumor Volume in 137 Patients With Small to Medium-Sized Vestibular Schwannoma

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Abstract

Objective. The video head impulse test (vHIT) and cervical and ocular vestibular evoked myogenic potentials (cVEMP and oVEMP) are new methods for measuring peripheral vestibular function. The objectives of this study were to compare these tests and the traditionally used caloric test in patients with small and medium-sized untreated vestibular schwannoma (VS) and to measure the correlation between the tests' results and tumor volume.

Study Design. National cross-sectional study.

Setting. Tertiary university clinic.

Methods. Prevalence of abnormal cVEMP, oVEMP, caloric test, and 6-canal vHIT results on the tumor side and the nontumor side were compared and related to tumor volume with regression analyses in 137 consecutive VS patients assigned to a wait-and-scan protocol in the period 2017 to 2019.

Results. The sensitivity of 6-canal vHIT, caloric test, cVEMP, and oVEMP to detect vestibulopathy in VS patients was 51%, 47%, 39%, and 25%, respectively. Normal tests were found in 21% of the patients. The results of vHIT and caloric test were related to tumor volume, but this was not found for cVEMP and oVEMP.

Conclusion. The caloric test and 6-canal vHIT showed the highest sensitivity in detecting vestibulopathy in untreated VS patients. vHIT, and particularly the posterior canal, was limited with a high prevalence of abnormal results on the nontumor side. A combination of cVEMP and caloric test was favorable in terms of a relatively high sensitivity and low prevalence of abnormal results on the nontumor side. Larger tumors had a higher rate of pathology on caloric testing and vHIT.

Keywords

caloric test, cVEMP, oVEMP, vestibular schwannoma, vestibular tests, vHIT, volume

Received February 24, 2023; accepted May 20, 2023.

In recent years, methods have been developed that allow detailed functional assessment of the vestibular end organs, particularly the video head impulse test (vHIT)[1] and recordings of cervical -and ocular vestibular evoked myogenic potentials (cVEMP and oVEMP, respectively).[2] These methods complement the caloric, which mainly test the function of the lateral semicircular canal (LSC),[3] and have the potential for more widespread clinical use. However, they are still undergoing development and standardization. Their sensitivity and specificity for objective vestibular lesions that can be verified and quantified by other methods, such as imaging, need to be determined.

Vestibular schwannoma (VS) is a benign tumor on the vestibular nerve. It is unique among vestibular disorders in that the vestibular loss, and the symptoms of the patient, are caused by pathology that can be easily visualized, localized, and measured on magnetic resonance imaging (MRI). Still, we are not able to predict dizziness or any other patient symptom based on MRI.

Some studies have found a relation with tumor size and vestibular nerve function. Impairment of vestibular nerve function could be due to the VS itself, mechanical factors, impaired blood supply to the vestibular nerve, biochemical factors, or a combination of these.

However, as shown in a previous study,[4] the correlation between tumor size and vestibular nerve function is not perfect. A small tumor (<10 mm) within the internal

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auditory canal may compress the vestibular nerve and cause vestibular loss at an early stage. Conversely, a larger tumor (15-25 mm) within the cerebellopontine angle may have more space to expand without compressing the nerve, and the vestibular function may be intact. Newer findings show that VS-secreted factors can lead to cochlear damage[5] and vestibular damage could, therefore, also be hypothesized and possibly explain the imperfect relation between tumor size and vestibular nerve function. Still, tumor volume is one hallmark of VS that can be easily measured. In this study, we are using a VS as a model to understand more about the new vestibular tests, their interpretation, and how VS affects various aspects of vestibular function.

The purpose of the study was to compare different tests of vestibular function on the tumor side and nontumor side among patients with untreated VS, and to measure the correlation between test results and tumor volume.

Method

Ethics

The study was approved in 2017 by the Regional Committees for Medical Research Ethics South East Norway (2017/765/REK sør-øst C) REK South East and informed consent at inclusion was obtained from all patients.

Design and Setting

A national cross-sectional study of patients with MRI confirmed VS referred to a tertiary university clinic for newly diagnosed untreated VS enrolled in the period June 2017 to June 2019.

Subjects

Consecutive patients with small to medium-sized tumors (≤25 mm in the cerebellopontine angle on MRI) assigned to a wait-and-scan protocol were included. Exclusion criteria were bilateral VS, intracochlear VS, and failure to complete the vestibular function tests consisting of air-conducted cVEMP, bone-conducted oVEMP, bithermal caloric test, and vHIT of all semicircular canals.

Caloric test

All patients underwent standard bithermal caloric tests with water. Canal paresis was defined as >25% % difference between left and right ears according to Jongkees' formula.[6]

vHIT

The function of the lateral, anterior, and posterior semicircular canals was measured using an ICS Impulse device (Otometrics, Natus Medical) that evaluates the gain of the vestibulo-ocular reflex (VOR) and allows visualization of catch-up saccades. A pair of lightweight goggles, containing a gyroscope to measure head velocity and a small high-speed video camera to measure eye movements, was firmly attached to the patient's head. In the plane of each semicircular canal, approximately 10 rapid head impulses of about 10° to 20° were randomly delivered while the patient was instructed to fixate the gaze to a stationary dot on the wall 1 to 1.2 m in front. Care was taken not to touch the goggles during testing.

Mean VOR gain for each semicircular canal was automatically measured in the integrated software as the ratio of the area under the eye velocity curve to the area under the head velocity curve. According to the producer, a mean gain <0.8 is considered abnormal for horizontal head impulses, and a mean gain <0.7 is abnormal for vertical head impulses. Four authors (F.K.G., K.S.N., J.E.B., and S.H.G.N.), blinded to tumor location and other test results, independently characterized the vHIT test as pathologic based on an abnormal gain or pathologic saccades. When the results were not equally rated, consensus was reached in the group. Corrective saccades with a velocity ≥50°/s occurring in ≥80% of head impulses were considered abnormal.[7]

cVEMP and oVEMP

VEMPs were determined using an Eclipse device (Interacoustics). Sound and vibration were used to stimulate the sacculus and utriculus, respectively, in order to produce a measurable reflex response. Repeatability was ensured by attempting to achieve 2 similar responses for each trial. The asymmetry ratio was calculated based on the formula

$$\frac{\text{Largest amplitude} - \text{Smallest amplitude}}{\text{Amplitude right side} + \text{Amplitude left side}}.$$

cVEMP

Patients were seated and instructed to turn their heads to one side to contract the sternocleidomastoid muscle on the opposite side. Air-conducted tone bursts were delivered to the ear ipsilateral to the contracted muscle with a frequency of 500 Hz and stimulus intensity of 100 dB normal hearing level. The patients were instructed to keep muscle contraction within the target range as visualized by a red/green bar on an electromyography (EMG) display. EMG weighting was applied to compensate for unequal muscle contraction on the left and right sides.[8] For the cVEMP amplitude, an asymmetry ratio ≥0.30 was considered abnormal.[9]

oVEMP

Bone-conducted stimuli, "minitaps," by use of a handheld minishaker (type 4810; Brüel & Kjaer) held perpendicular in the midline of the patient's hairline without adding force, were used to elicit the reflex while the patient was

asked to look upward. The reflex response was recorded from the contralateral inferior oblique muscle through surface electrodes beneath the eyes. A power amplifier, type 2718 Brüel & Kjaer, was used. An asymmetry ratio ≥ 0.39 was considered abnormal.[9]

Radiological Characteristics

Observer-blinded volumetric tumor measurements were performed on the diagnostic MRI using iPlan Brainlab Elements (Version 3.3; Brainlab AG), as described in an earlier study.[10] Two of the authors (D.D. and K.S.N.) measured and Koos-classified the tumors[11]:

Grade I = small intracanalicular tumor. Grade II = small tumor with protrusion into the CPA; no contact with the brainstem. Grade III = tumor occupying the cerebellopontine cistern with no brainstem displacement. Grade IV = large tumor with brainstem and cranial nerve displacement. We also registered the largest diameter on axial MRI.

Statistics

Continuous variables are presented with mean, standard deviation, confidence interval (CI), median, range, and interquartile range. Categorical variables are presented as counts and percentages. VEMP responses were classified as pathologic (yes/no) based on the asymmetry ratio. Lack of response in one side resulted in an amplitude of 0 and consequently an asymmetry ratio of 1. The absence of responses on both sides resulted in no pathologic level of asymmetry ratio. VEMP amplitude was registered. The 6-canal vHIT was categorized as abnormal if vHIT from at least one of the semicircular canals was pathologic. Unadjusted linear regression analysis was used to assess the relationship between vHIT gain and tumor volume for each canal separately, and for canal paresis and tumor volume. Unadjusted logistic regression analysis was performed to assess the relationship between saccades (yes/no) and tumor volume, and pathologic VEMP (yes/no) and tumor volume. p values less than .05 were considered statistically significant. Statistical analyses were performed using Stata Software (Version 17.0 StataCorp).

Results

Demography and Tumor Data

One hundred thirty-seven patients fulfilled the inclusion criteria. A summary of demographics and tumor data is shown in **Table 1**.

Table 1. Descriptive Data of 137 Patients With Untreated Vestibular Schwannoma

Parameter	Values
Age, y (mean, SD)	55.4, 11.2
Female (n, %)	73, 53.3
Tumor volume, mm^3 (median, IQR)	255, 390
Koos grade	
Koos grade 1 (n, %)	59, 43
Koos grade 2 (n, %)	67, 49
Koos grade 3 (n, %)	11, 8
Tumor size (maximum diameter, mm) (mean, SD)	10.5, 4.7
Right-sided tumor (n, %)	58, 42.3

Abbreviations: IQR, interquartile range; n, count; SD, standard deviation.

Overview of Vestibular Test Results

Prevalence of abnormal test results for each test and combinations of tests on the tumor side and nontumor side are shown in **Table 2**. Scatterplots including cut-offs for abnormal test results in right- and left-sided tumors for cVEMP, oVEMP, 6-canal vHIT, and caloric test are presented in **Figure 1**. The relationship between canal paresis and vHIT lateral canal gain is shown in **Figure 2**. Given a normal caloric test on the tumor side, the sensitivity for detecting a tumor of the 6-canal vHIT, LSC vHIT, anterior semicircular canal (ASC) vHIT, posterior semicircular canal (PSC), cVEMP, and oVEMP was 30.6%, 9.7%, 8.3%, 22.2%, 33.3% and 19.4%, respectively.

Relation of Vestibular Test Results and Tumor Volume

Figure 3 shows the relationship between caloric asymmetry on the tumor side and tumor volume (mm^3). Linear regression analysis showed a significant relationship between canal paresis on the tumor side and tumor volume (cm^3) (coeff. 20, 95% CI: 8.7-31.3; $p = .001$).

LSC gain was related to tumor volume (coeff. −0.08, 95% CI: −0.15 to −0.02; $p = .012$). There was no significant association between saccades in the LSC and tumor volume ($p = .42$). PSC gain was related to tumor volume (coeff. −0.09, 95% CI: −0.16 to −0.02; $p = .016$). For the PSC, the odds for saccades were significantly higher for tumors larger than 0.475 cm^3 (odds ratio [OR] = 2.3, 95% CI: 1.05-5.13; $p = .037$). ASC gain was related to tumor volume (coeff. −0.06, 95% CI: −0.11 to −0.01; $p = .03$). There was no significant association between saccades for the ASC and tumor volume ($p = .861$). Performing unadjusted logistic regression analysis, there was no significant association between abnormal cVEMP on the tumor side and tumor volume or between abnormal oVEMP on the tumor side and tumor volume.

Discussion

Main Findings

This study found that the caloric test and the 6-canal vHIT were the most sensitive tests in detecting vestibulopathy in patients with untreated small to medium-sized VS. However, vHIT of the posterior canals was frequently abnormal on both sides or the nontumor side. cVEMP

Table 2. Sensitivity and Percentage of Abnormal Test Results Related to Tumor Side in 137 Patients With Untreated Vestibular Schwannoma

		% abnormal results related to tumor side		
Abnormal vestibular test	Sensitivity[a] (%)	Tumor side	Both sides	Nontumor side
Caloric	47	47	0	2
vHIT lateral	28	23	5	4
vHIT anterior	16	15	1	1
vHIT posterior	41	31	10	7
cVEMP[b]	39	39	0	4
oVEMP[b]	25	25	0	3
Any vHIT[c]	51	36	15	8
Caloric or cVEMP[b]	65	64	1	5
cVEMP or oVEMP[b]	52	51	1	6
cVEMP[b] or vHIT posterior	60	46	14	7
Caloric or vHIT lateral	53	47	6	5
Caloric or any vHIT[c]	64	47	17	8
Any of all tests[b]	79	56	23	8

Abbreviations: cVEMP, cervical vestibular evoked myogenic potentials; oVEMP, ocular vestibular evoked myogenic potentials; vHIT, video head impulse test.
[a]Sensitivity defined as abnormal result on tumor side or both sides.
[b]Bilateral absent VEMP responses defined as normal.
[c]Abnormal vHIT in at least 1 semicircular canal.

was more sensitive than oVEMP, and both tests had a low percentage of abnormal tests on the nontumor side. Performing cVEMP together with the caloric test increased the sensitivity to 65% while keeping abnormal results on the nontumor side low.

Comparison With Previous Studies in VS Patients

It is important that reports on sensitivity also consider the nontumor side. In the study of Lee et al with 101 VS patients,[12] VOR impairment was reported with vHIT on the ipsilesional side in 80%, on the contralesional side in 43% of patients and bilaterally in 42%. Bilaterally, VOR impairment correlated with tumor size. Absent VEMP responses were registered for ipsilesional and contralesional sides; asymmetry ratios were not used. In the literature, the sensitivity of vestibular tests in VS patients has mainly been determined with only some of the vestibular tests in each study, diverse methods, diverse definitions of a pathologic result, and different tumor sizes, thus it is difficult to compare the sensitivities of the tests related to each other. The sensitivities are reported to be 62% to 72% for the caloric test,[4,13,14] 27% to 90% for lateral canal vHIT,[9,12-15] 50% to 73% for oVEMP,[9,16,17] and 50% to 79% for cVEMP.[9,16,18] Lateral and posterior canal vHIT have been found to be more sensitive than anterior canal vHIT,[9,15,19] with sensitivities ranging from 27% to 57% and 8% to 36%, respectively. We generally found lower sensitivities than reported in the literature and this could be due to the smaller tumor size in our study. In our study mean maximum tumor diameter was 10.5 mm and 92% of the patients had tumors with Koos-grade 1-2. Other studies report tumor sizes in different ways. Hannover-classification: ≥42% of the VS in the studies[12,20] were T3 and T4 tumors. Koos-grade[15,21]: Koos-grade 1-2 and Koos-grade 3-4 were reported in 72% to 82% and 28% to 18% of the patients, respectively. Mean tumor size: 2 studies[14,19] included VS patients with mean tumor diameter of 9.2 to 12.2 mm, while 19.3 to 21.3 mm was the mean tumor size in the other 2 studies[9,17] using this measure. West et al[18] mainly investigated tumors with maximum diameter of 11 to 30 mm, and in the study of Zhou et al[16] 75% had maximum tumor diameter from 15 to >30 mm.

Tumor Size May Influence Test Sensitivity

We found that the sensitivity of vHIT and caloric test in detecting a VS is volume-dependent.

Several previous studies have found an association between larger tumors and one or more of canal paresis, lower vHIT gain/gain asymmetry, increased prevalence of vHIT saccades and VEMP pathology,[4,9,12,21-19,16,22] while some of the associations were not found. One might think that small tumors growing in the internal auditory meatus cause increasing compression on the nerve, but with larger tumors, the internal auditory meatus may already be obliterated by the tumor and the main growth may be in the posterior fossa where the effect on the vestibular function becomes more unpredictable.

Other Factors That May Have an Impact on VEMP and vHIT Sensitivity

About 10% of the patients showed no response of cVEMP or oVEMP on either side. This was interpreted as a normal finding. Studies on healthy controls have shown a decreased cVEMP response rate at age >60 years.[23]

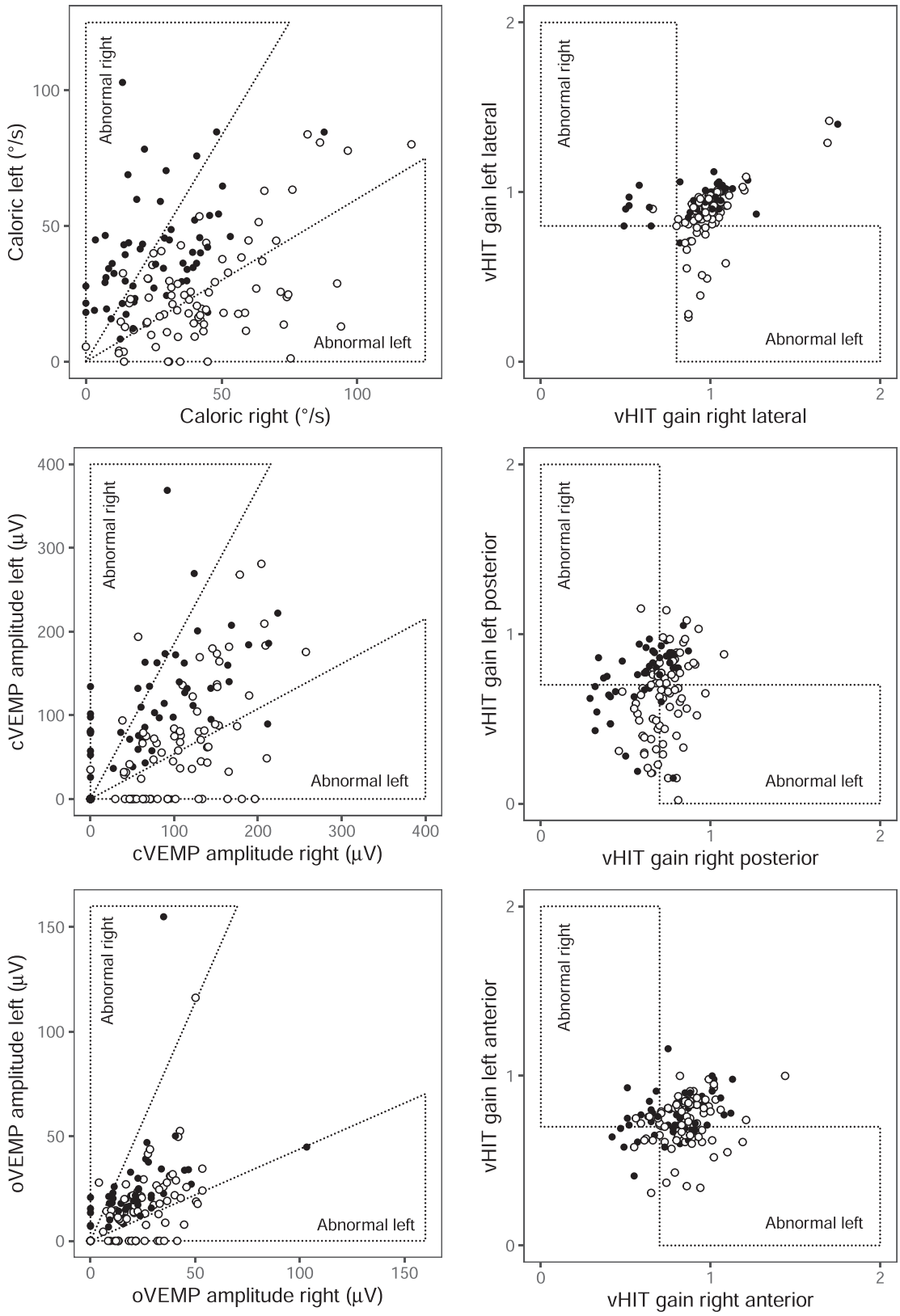

Figure 1. Vestibular test results in 137 patients with untreated small to medium-sized vestibular schwannoma. Black and white dots indicate patients with right- and left-sided tumors, respectively. Dotted areas indicate abnormal results defined as asymmetry greater than 25%, 30%, and 39% for caloric response, cVEMP, and oVEMP, respectively, or unilaterally abnormal vHIT gain less than 0.8 for the lateral canals or 0.7 for the vertical canals. A few individuals with abnormal results on the nontumor side are seen as white dots in the upper or black dots in the lower dotted closed areas. Caloric left/right: Maximum slow phase velocity of nystagmus induced by water irrigation (sum of warm + cold water responses). cVEMP/oVEMP, cervical/ocular evoked myogenic potentials; vHIT, video head impulse test.

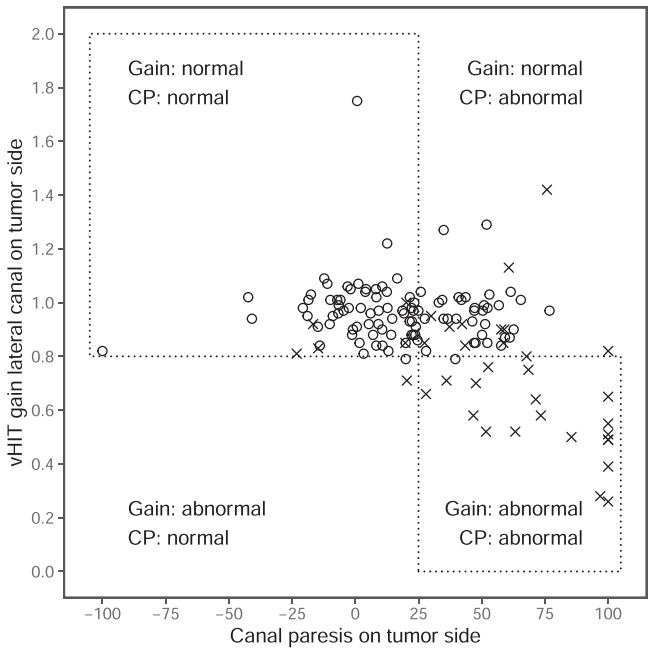

Figure 2. Scatterplot showing the relationship between vHIT lateral canal gain and canal paresis on the tumor side in 137 untreated VS patients. CP, canal paresis; Cross, with catch-up saccades; dots, without catch-up saccades; vHIT, video head impulse test; VS, vestibular schwannoma.

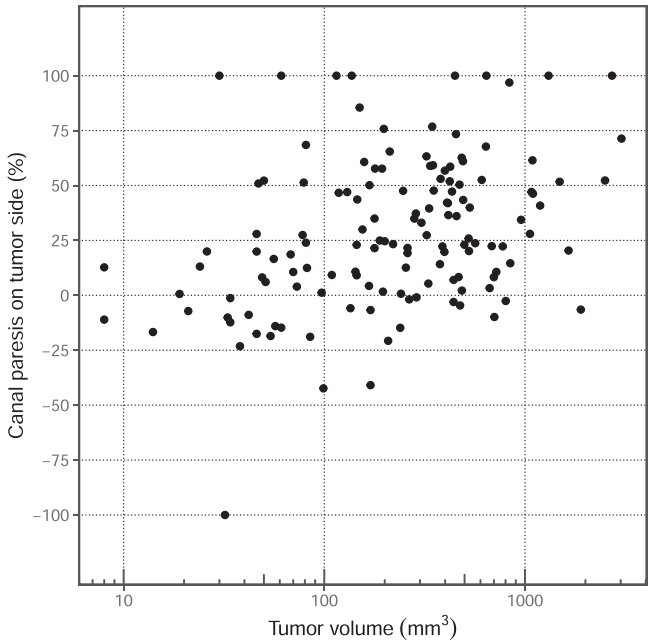

Figure 3. Scatterplot showing the relationship between caloric asymmetry on the tumor side (%) and markings of tumor volume (mm^3) on a logarithmic scale.

It may be difficult to obtain a good trade-off between sensitivity and specificity when setting clinical cutoff values. This is demonstrated in the scatterplots in **Figure 1**, where the normal limits are marked. Variations in test methods and the definition of a pathologic result also influence the sensitivity. vHIT gain can be measured by different methods and the definition of a pathologic vHIT result also varies. Some authors require both a pathologic saccade and pathologic gain, others require only one them. For VEMP, most authors use a cutoff for abnormal asymmetry ratio, while others use absent VEMP response (yes/no). For vHIT, there are potential challenges in separating an abnormal or normal result from an artefact.[24] We found a significant prevalence of saccades on the nontumor side, in accordance with other studies.[12,21] This finding is physiologic[1]; however, the saccades to the healthy side can cause difficulties with interpretation, and thus explain some of the abnormal vHIT results on the nontumor side in our study. Tranter-Entwistle et al[13] found that canal paresis could be predicted from not only ipsilesional, but also contralesional vHIT gains. A subjective evaluation of vHIT results from both sides considered together will probably result in more pathology on one side relative to the other. To minimize artefacts, correct execution of the head impulses is critical. There is a learning curve as well as patient-related issues related to neck mobility, voluntary movements, blinking, and mask slippage. For these reasons, the execution and interpretation of vHIT are probably more dependent on an experienced user compared to a caloric test.

Effect of Combining the Vestibular Function Tests

Our results (**Table 2**) suggest that vestibular function tests both overlap and complement each other. This is as expected as VS tumors vary in size and location, comprising a diverse amount of afferent nerve fibers coming from the 5 vestibular end organs.

A possible reason for our finding of a high prevalence of normal nerve function despite a VS might be that the VS does not necessarily affect the vestibular nerve fibers, only surround it, or does not affect the nerve enough to exceed the test's normal limit.

The combination of cVEMP and caloric test seems to be a reasonable choice in detecting vestibulopathy in the inferior and superior nerves due to the relatively high sensitivity and the low prevalence of abnormal tests on the nontumor side. Performing all tests increases the sensitivity, but also the prevalence of abnormal results on the nontumor side and both sides (**Table 2**), making the clinical applicability more questionable.

Our results suggest that if the caloric test is normal, lateral canal vHIT does not provide additional information (**Figure 2** and **Table 2**). The caloric test and lateral canal vHIT measure afferent nerve fibers from the lateral canal. The difference in sensitivity might be explained by testing at low frequencies in the caloric test and high frequencies in vHIT.

Strengths and Limitations

To our knowledge, this is the first study to compare 6-canal vHIT, cVEMP, oVEMP, and caloric test on the

tumor side and nontumor side in untreated VS patients and relate the tests' sensitivity to tumor volume, which is the most reliable measure of tumor size.[25] VS patients have a chronic disease and often have a compensated or good vestibular function. Thus, the results from our study cannot necessarily be generalized to other acute or episodic vestibular diseases like vestibular neuritis and Ménière's disease. We examined small to medium-sized schwannomas and the results are not necessarily representative for larger tumors.

Implications

As vestibular compensation may explain why many VS patients have few vestibular symptoms despite an objective reduced function,[10] a detailed examination of the vestibular nerve's function may increase the knowledge of how vestibular function, vestibular symptoms, and central compensation are related. This knowledge could be valuable when tailoring postoperative vestibular therapy in VS patients. Patients with a better function of the vestibular nerve before surgery are probably those that will need physiotherapy the most, and may be candidates for prehab treatment with gentamycin injections. This study illustrates that vHIT, in particular, shows a high rate of pathology on the healthy side, and that the interpretation of these tests can be challenging. Future research should compare vestibular tests in different vestibulopathies and focus on developing a standard for the interpretation of vHIT and VEMP.

Conclusion

In this study, the caloric test and 6-canal vHIT had the highest sensitivity. One limitation with vHIT was the high prevalence of abnormal results on both sides, particularly for the posterior canal, and performing a lateral canal vHIT in patients with a normal caloric test did not provide additional information. The combination of caloric test and cVEMP resulted in a relatively high sensitivity and a high degree of correct identification of tumor side. Performing all tests slightly increased the sensitivity; however, the prevalence of abnormal tests on the nontumor side increased considerably.

Acknowledgments

The authors would like to thank study nurses Sofia Ekström and Ingelin Økland Bø for their valuable contribution to the project.

Author Contributions

Kathrin Skorpa Nilsen, design, data collection, measurement of tumor volume, analysis, interpretation of data, drafting and revising the manuscript for important intellectual content; final approval of the version to be published and presentation of the research (abstract accepted for poster presentation at AAO-23); **Stein Helge Glad Nordahl**, design, interpretation of data, revising the manuscript for important intellectual content; final approval of the version to be published; **Jan Erik Berge**, interpretation of data and revising manuscript for important intellectual content; final approval of the version to be published; **Dhanushan Dhayalan**, measurement of tumor volume and revising manuscript for important intellectual content; final approval of the version to be published; **Frederik Kragerud Goplen**, design, data collection, analysis, interpretation of data, drafting and revising the manuscript for important intellectual content; final approval of the version to be published.

Disclosures

Competing interests: None.

Funding: None.

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