Vestibular Symptoms, Balance and Vestibular Function in Patients with Vestibular Schwannoma

Kathrin Skorpa Nilsen

Thesis for the degree of Philosophiae Doctor (PhD)
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1. Abbreviations

ABR	Auditory Brainstem Response
°C	Degrees centigrade
c-and oVEMP	Cervical and ocular vestibular evoked myogenic potentials
CDP	Computerized dynamic posturography
CL	Cold left
CR	Cold right
COP	Center of pressure
CPA	Cerebellopontine angle
CT	Computed tomography
EMG	Electromyography
ENT	Ear- nose- and throat
GBI	Glasgow benefit inventory
GKR	Gamma knife radiosurgery
HUS	Haukeland University Hospital
IVN	Inferior vestibular nerve
MRI	Magnetic resonance imaging
MS	Microsurgery
PhD	Degree philosophiae doctor
PTA	Pure tone average
PPPD	Persistent postural-perceptual dizziness
REK	Regional committee for medical and health research ethics
SD	Standard deviation
SF-36	Short-form 36 health status questionnaire
SOT	Sensory organization test
SVN	Superior vestibular nerve
VDT	Volume doubling time
vHIT	Video head impulse test
VS	Vestibular schwannoma
VAS	Visual analog scale

VOR	Vestibular ocular reflex
WR	Warm right
WL	Warm left
WRS	Word recognition score

2. Scientific Environment

This work has been performed at the National Advisory Unit on Vestibular Disorders in collaboration with the Department of Clinical Medicine at the University of Bergen. Dr. Frederik Kragerud Goplen has been my main supervisor while Dr. Stein Helge Glad Nordahl and Dr. Morten Lund Johansen have been my co-supervisors during the PhD program. The National Advisory Unit on Vestibular Disorder is located at the Balance Laboratory, Department of Otorhinolaryngology, at Haukeland University Hospital (HUS). As The Norwegian National Unit for Vestibular Schwannomas is a collaboration between the Department of Otorhinolaryngology and the Department of Neurosurgery at HUS, nearly all patients with vestibular schwannoma in Norway are referred to the Balance Laboratory for vestibular testing.

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Haukeland University Hospital

Norwegian National Advisory Unit
on Vestibular Disorders

3. Acknowledgements

First of all, I would like to express my gratitude for being given the opportunity to be a PhD candidate at the Norwegian National Advisory Unit on Vestibular Disorders. I was introduced to neurotology through my clinical work at the Department of Otorhinolaryngology at Haukeland University Hospital and was fascinated and horrified at the same time about the complex diseases occurring in the vestibular apparatus. The more complex the case, the more enthusiasm Dr. Goplen and Dr. Nordahl showed when they were consulted. In their pursuit of diagnosing and treating challenging cases it was sometimes necessary to search through literature, and occasionally this could give rise to a research idea which they then brought to life. This approach picked out my interest in the field, and I hope to maintain this curiosity throughout my clinical and scientific career.

I am especially grateful to my excellent main supervisor, Dr. Frederik Kragerud Goplen, who has taught me a lot about neurotology and scientific skills. He always has an answer to difficult research or clinical questions, and he has inspired me to learn more about neurotology. His detailed review of articles and helpful tips for oral presentations have been highly valuable.
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Thanks to my parents, brother and sister for giving me the best childhood, and especially my parents for your wise advice, support and always being there to help. I am also grateful for the support from my parents-in-law. Lastly, I want to thank my dear husband Rune for your constant love and support. I am grateful to share my life with you and our lovely children Heine, Sofie and Louise.

4. ABSTRACT

Background: Vestibular schwannoma (VS) is a benign tumor on the 8th cranial nerve that often leads to hearing loss, tinnitus, unsteadiness and vertigo. Treatment is based on tumor size or whether there is growth of tumor, and includes either observation (wait-and-scan), radiosurgery or microsurgery. Little is known about the natural course of the disease when it comes to vestibular symptoms and function.
Aim: To study how vestibular symptoms and function are affected by untreated VS, in a short- and long-term perspective.
Material and methods: Patients with newly diagnosed untreated VS were included in the periods 2001-2010 and from June 2017 to June 2019. A cohort followed up regularly for up to ten years and a cross-sectional study, respectively.
Results: No dizziness was reported by 35% of the patients. Moderate to severe dizziness was reported by 31% and was associated with canal paresis and postural instability. In the subgroup with no growth of tumor during follow-up (N=114) we found no significant increase in dizziness, postural unsteadiness or canal paresis. Furthermore, unsteadiness on posturography predicted tumor growth within 3 years (OR= 5.6, 95 % CI 2.6, 11.8). The 6-canal video head impulse test (vHIT) and the caloric test were the most sensitive tests with sensitivities of 51% and 47 %, respectively. Posterior canal vHIT often showed abnormal results on the non-tumor side (17%). The combination of caloric test and cervical vestibular evoked myogenic potentials (cVEMP) increased the sensitivity to 65%, while only a few had abnormal tests on the non-tumor side (6%).
Conclusions: The majority of untreated VS patients experienced either no dizziness or only mild symptoms. Our findings suggest a favorable long-term prognosis for vestibular symptoms and functions in patients managed through a wait-and-scan approach without tumor-growth. The presence of unsteadiness, as measured by posturography, predicted tumor growth in untreated VS patients within three years. An implication of this could be that unsteady patients need more active management. The combination of caloric test and cVEMP was most useful, due to the relatively high sensitivity and low prevalence of abnormal tests on the non-tumor side.

5. Sammendrag (abstract in Norwegian)

Bakgrunn: Vestibularisschwannom (VS) er en godartet svulst på den 8.hjernenerve som ofte fører til hørselstap, øresus, ustøhet og vertigo. Behandling avhenger av svulstens størrelse og om svulsten vokser, og inkluderer enten observasjon (wait-and-scan), stråling eller operasjon. Man vet lite om det naturlige forløpet av sykdommen når det gjelder vestibulære symptomer og funksjon.
Mål: Å undersøke hvordan vestibulære symptomer og funksjon påvirkes av et ubehandlet VS, både på kort og lang sikt.
Materialer og metode: Pasienter med nylig diagnostisert, ubehandlet VS ble inkludert i periodene 2001-2010 og fra juni 2017 til juni 2019; henholdsvis en gruppe pasienter som ble fulgt opp regelmessig i inntil ti år og en tverrsnitts studie.
Resultater: Ingen svimmelhet ble rapportert av 35% av pasientene. Moderat til alvorlig svimmelhet ble rapportert hos 31% og var assosiert med kanal parese og postural ustøhet. I gruppen uten vekst av tumor i oppfølgningsperioden (N=114) fant vi ikke signifikant økning av svimmelhet, postural ustøhet eller kanal parese. Vi fant videre at ustøhet ved posturografi predikerte vekst av tumor innen 3 år (OR=5,6 og 95% CI 2,6-11,8). 6-canal video hode impuls test (vHIT) og kalorisk prøve var de mest sensitive testene med sensitivitet på henholdsvis 51% og 47%. vHIT av posteriore kanal var ofte abnormal på den friske siden (17%). Kombinasjonen av kalorisk prøve og cervicale vestibulære myogene potensialer (cVEMP) økte sensitiviteten til 65% samtidig som bare noen få hadde abnormal test på non-tumor siden (6%).
Konklusjoner: Majoriteten av ubehandlede pasienter med VS opplevde enten ingen svimmelhet eller kun milde symptomer. Funnene våre indikerer en god prognose når det gjelder vestibulære symptomer og vestibulær funksjon hos pasienter som behandles konservativt i form av wait-and-scan. Ustøhet målt på posturografi, predikerte vekst av svulsten innen 3 år hos pasienter med ubehandlet VS. En konsekvens av dette kan være at ustødige pasienter trenger mer aktiv oppfølgning. Kombinasjonen av kalorisk prøve og cVEMP var den mest nyttige, noe som skyldtes en relativ høy sensitivitet og en lav andel av abnormale resultat på den friske siden.

6. List of Publications

1. Andersen, J.F., Nilsen, K., Vassbotn F.S., Møller, P., Myrseth, E. Lund-Johansen, M. & Goplen, F. (April 2015). “Predictors of vertigo in patients with untreated vestibular schwannoma.” Otology & Neurotology, 36(4):647-652.

2. Nilsen, K., Lund-Johansen, M., Nordahl, S.H.G., Finnkirk, M., Goplen, F.K. (July 2019). “Long-term effects of conservative management of vestibular schwannoma on dizziness, balance and caloric function”. Otolaryngology-Head and Neck Surgery, 161 (5):846-851.

3. Nilsen, K., Dhayalan D., Lund-Johansen M. & Goplen F.K. (April 2021). “Postural sway predicts growth in untreated vestibular schwannoma: A retrospective volumetric study”. Otology & Neurotology, 42(4):e495-e502

4. Nilsen, K., Nordahl, S.H.G., Berge, J.E., Dhayalan D. & Goplen F.K. (June 2023). “Vestibular tests related to tumor volume in 137 patients with small to medium-sized vestibular schwannoma”. Otolaryngology-Head and Neck Surgery, Online ahead of print.

7. Contents

8. INTRODUCTION

8.1 Vestibular schwannoma

Vestibular schwannoma (VS) is a benign tumor considered to arise from Schwann cells of the vestibular part of the 8th cranial nerve.[1] The most common symptoms in untreated VS patients are unilateral hearing loss, tinnitus, unsteadiness and vertigo.[2-9] Today, the tumors are smaller when they are discovered,[10] and one rarely has to deal with the large life-threatening tumors described a century ago. Since that time, the focus of treatment has shifted towards preservation of cranial nerves, especially the auditory and facial nerves, and quality of life. Increasing hearing loss has been the major concern related to tumor growth and timing of treatment. Implications for vestibular function and vestibular symptoms have been less studied.

"It is easy to underrate the importance of a sensory system whose receptor is buried deep within the skull and of whose performance we are usually notaware"[11]

8.1.1 History

Historically, the development of the neurosurgeon's VS operation techniques and ENTs' discovery and advancement of audiovestibular physiology occurred mainly in parallel, without any collaboration between the two disciplines. In the 1950s, the neurosurgeons and ENTs started to collaborate concerning VS patients, which led to further improvement in diagnosis and treatment.[12]

Neurosurgeons and ENTs advance in their respective fields in the diagnosis and management of VS

The first postmortem description of a vestibular schwannoma was described in 1777 by Eduard Sandifort of Leiden in the paper "De duro quodam corpusculo, nervo auditorio adherente" ("Regarding a certain hard body adherent to the auditory nerve").[13,14] Through the 19th century, the diagnosis of VS improved. Patients had

otologic symptoms such as unilateral hearing loss and giddiness, but the picture was dominated by neurological symptoms such as anesthesia of the trigeminal nerve, headache, vomiting and, eventually, brainstem failure and death. The neurosurgeon Annandale was considered by many to be the first to perform successful removal of a VS in 1895.[15] During the 20th century, the number of VS surgeries increased, but the mortality rate was high. Harvey Cushing and later Walter Dandy were famous neurosurgeons, treating VS at that time to preserve life.[12,14,16]

In the mid-19th century, vertigo was thought to be caused by the overfilling of blood vessels in the brain. The inner ear's function in maintaining postural control and orientation was not known.[17] The first discovery of the vestibular system was by Flourens in 1824.[18] He injured pigeons' semicircular canals and found that this caused serious disorders of the equilibrium, but it was not until Prosper Menière utilized Flourens' discovery that it was understood that inner ear disease could cause vertigo in humans.[19] The vestibular physiology was further understood when Robert Bárány recognized that nystagmus could indicate vestibular pathology. He described the caloric test (Figure 1) in 1906 and for this he received the Nobel Prize in 1916.[20] Otologists could now detect a VS before the patients developed neurological symptoms. A patient with reduced function of the vestibular nerve, together with reduced hearing on the same side, was a strong indicator of a VS. The lack of impaired balance would suggest a slowly growing tumor. The development of the Bekesy Audiometry and Speech Audiometry in the 1940s revealed hearing asymmetry, and thus put the doctor on the trail of a VS.

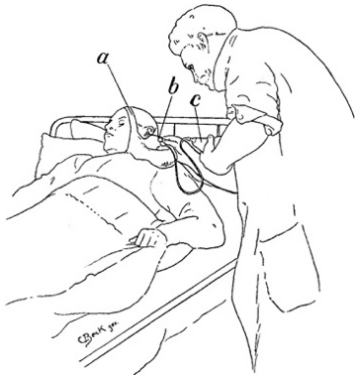

Figure 1. Illustration of Robert Bárány's caloric test from his 1907 book.
a) Collection basin, b) catheter for infusing the water, and c) inflatable rubber bag for injecting the water.[20,144]

Development of the Otoneurosurgical team in the 1950s

The otolaryngologist Bill House started to collaborate with neurosurgeons on the diagnosis and treatment of VS in the 1950s, and in 1961 he operated on his first patient together with Doyle, a neurosurgeon.[12] House brought VS surgery to a new level by introducing the operating microscope. With the advancement of radiology, with CT scanners in the 1960s and MRI in the 1980s, VS surgery improved.

In the 1960s, the focus of surgery was on preservation of the facial nerve. In the 1970s, the diagnosis was often made solely on the basis of otological symptoms and signs, such as hearing loss, tinnitus, dizziness, and vertigo. Because the tumor was now being discovered when it was smaller, the patients could be operated on while still in good condition.[12] The use of auditory brainstem response (ABR) was suggested from the 1970s.[21]

Lars Leksell, a Swedish neurosurgeon and professor, introduced the Gamma Knife in the early 1970s. The combination of stereotaxy and gamma radiation made it possible to treat the VS and other intracranial pathologies. Radiation was given from different angles, with the focal point within the tumor, exposing the surrounding tissue with only low doses of radiation.[12,14,16] Later, other vendors have developed different devices for stereotactic radiosurgery, like CyberKnife. Fractionated radiotherapy or hypofractionated stereotactic radiotherapy are also used.[22]

Management of VS at Haukeland University Hospital

Haukeland University Hospital (HUS) received the Gamma Knife® unit in 1988, as the fifth country in the world to do so, and the only one in Norway since that time. From 2012, HUS was given national treatment responsibility for vestibular schwannomas. The ENT Department, together with the Balance Laboratory and the Department of neurosurgery at HUS, collaborate on VS management and research. Since 1986, these departments have worked together on the surgical treatment of VS patients,[23] with the otologist Per Möller as the first in Norway to perform translabyrinthine VS surgery, in 1976. The ENT department and the neurosurgery department have for many years collaborated with the Mayo Clinic in Rochester, Minnesota, on research of VS patients.

New vestibular function tests improve insight into the vestibular apparatus

In 1988, Halmagyi and Curthoys introduced the head impulse test,[24] which was further advanced to the video head impulse test in 2009.[25] The first testing of otolith organs with the vestibular evoked myogenic potentials (VEMP),[26] was performed in the 1960s. Before this, testing was rather cumbersome, and in particular very difficult to perform tests on a single side. As a clinical investigation it was utilized from the 1990s.[27,28] cVEMP was established as a test of saccular function and later, in the early 2000s, oVEMP was[29,30] found to be a test of utricular function. Since the 1990s, otolith testing has been performed at HUS. Ocular counter roll was eventually replaced by VEMP, which has the advantage of localizing unilateral pathology. The three vestibular tests vHIT, cVEMP and oVEMP are considered to be new tests, and further research is necessary to establish standardization of test methods and their use in different vestibular pathologies.

8.1.2 Epidemiology

The incidence of VS increased from 3/million/year to 34/million/year in Denmark in the period from 1976 to 2015. Possible explanations are improved screening control for unilateral hearing loss and easier access to MRI, thereby diagnosing more tumors in the elderly. More MRI imaging are also performed for other causes with a corresponding increase in incidental findings. In the same period, diagnostic tumor size decreased from 26 mm to 7 mm, and the age at diagnosis increased from 49 to 60 years.[10] A study by Marinelli et al. estimates the global incidence of a VS to be up to 50/million/year for all age groups, and up to 200/million/year among age groups at greatest risk.[31] The authors suggest that the chance of developing a VS during a lifetime probably exceeds 1 in 500.

8.1.3 Diagnostics

Today, MRI has replaced auditory brainstem response (ABR) in diagnosing a VS. Unilateral hearing loss and tinnitus are often the first symptoms that lead to the

suspicion of a VS.[2] The gold standard for diagnosing a VS is considered to be high-resolution contrast-enhanced T1-weighted MRI (Figure 2).[32,33] From the 1970s, auditory brainstem response (ABR) and computed tomography (CT) were used in the diagnosis of VS. With the improved availability and technique of MRI, ABR is less used as a screening method for VS. ABR has limitations in detecting an intracanalicular VS and cannot be performed in patients with a hearing loss greater than 70 dB.[33] In a Danish study from 2016, Rafique et al.[34] concluded that ABR is not valid as a VS screening tool, since the sensitivity was found to be 80% and the specificity was 77%. MRI was more cost-effective compared to ABR in Denmark.[34] On the other hand, Wijn et al.[35] found that ABR prior to MRI was cost-effective, but the authors questioned whether the cost reduction justified the risk of misdiagnosing patients with VS and other pathologies detectable only on MRI.

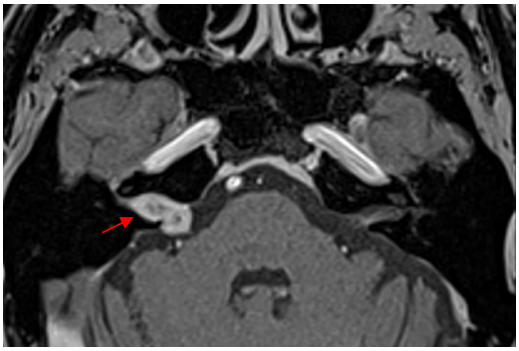

Figure 2. Contrast-enhanced T1-weighted MRI, axial view, demonstrating a vestibular schwannoma located in the internal auditory canal and protracting to the cerebellopontine angle, koos grade II.

8.1.4 Symptoms and implications

Patients report unilateral hearing loss (94-97 %), tinnitus (73-83%), unsteadiness (34-63%) and vertigo (20-49%).[2-9] Headache is experienced by 18-26%.[2,3] Large tumors may cause numbness and weakness of the face, and symptoms from brainstem compression and hydrocephalus.[22] Fatigue was present in 57% of VS patients in a study from Dhayalan et al[36] and vertigo, apathy, and depression were found to be predictors of fatigue.

The hearing loss is typically progressive, high-frequency loss accompanied by poor speech discrimination. Sudden hearing loss was reported by 10-20% of VS patients

during the course of observation[37] and occurred as a presenting symptom of VS in about 2%.[38]

Despite being a well-defined peripheral vestibular disorder, the severity and characteristics of vestibular symptoms vary widely, and are not completely understood. Carlson et al.[39] found that before treatment 34% of VS patients reported mild dizziness, 15% reported severe dizziness and 51% reported no dizziness. Seven years after treatment, dizziness was characterized as unsteadiness, vertigo, lightheadedness or nonspecific dizziness.[39] The degree of vestibular symptoms depends on the rapidity of the vestibular function loss.

The fact that dizziness, vertigo, and unsteadiness are nonspecific symptoms, and seem to be reported in different ways in the VS literature, makes it challenging to compare results and search for predictors of these symptoms. A study by Newman-Toker et al. found that patients are often inconsistent and change their description of dizziness quality when asked again only minutes later.[40] 62% of patients that reported dizziness in the study by Newman-Toker et al. also selected more than one type of dizziness.[40] Physicians also disagree on the meaning of the words "vertigo" and "dizziness".[41] In 2009, the Committee for the Classification of Vestibular Disorders of the Bárány Society decided to define key vestibular symptoms as the basis for an initial step towards the first International Classification of Vestibular Disorders (ICVD-I):[42]

Vertigo:

"Vertigo is the sensation of self-motion when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement."

Dizziness:

"Dizziness is the sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion."

Unsteadiness:

"Unsteadiness is the feeling of being unstable while seated, standing, or walking without a particular directional preference."

Nevertheless, vestibular symptoms are still subjective and perceived as a result of not only vestibular input, but also somatosensory and visual input.[43] There is no area in the cerebral cortex that only receives vestibular input.[44] The use of objective measures of vestibular function and objective measures of postural control will therefore add valuable information in evaluating how VS affects vestibular function and symptoms.

Long-term data on audiovestibular symptoms

Hearing loss is typically progressive[45,46] and the rate of hearing loss is similar in untreated patients and in those treated with Gamma Knife radiosurgery.[47] Additionally, the rate of decline in pure tone average (PTA) and decline in word recognition score (WRS) during the early period of observation are significant predictors of the time for development of non-serviceable hearing.[48] The long-term risk of losing serviceable hearing is relatively small if serviceable hearing is preserved for five years in patients with conservatively treated intracanalicular VS and the rate of hearing loss is greater for patients with a growing tumor.[49] Regarding tinnitus, Breivik et al. found no significant change in the occurrence of and intensity of tinnitus from baseline to last control in conservatively treated VS patients.[50]
In contrast to hearing outcome, there are only a few studies of long-term data for vestibular symptoms such as dizziness and imbalance in conservatively managed VS, and no long-term data on vestibular function and objective measure of postural balance. There was no significant change in subjective unsteadiness at last clinical control in the study by Breivik et al., but a significantly reduced number of patients with vertigo. The VAS score for vertigo did not change from baseline to last follow-up.[50]

Implications of vestibular symptoms

In a prospectively followed cohort of Norwegian patients with vestibular schwannoma, vestibular complaints were significant predictors of becoming dependent on disability pension. Vestibular symptoms were significantly more associated with disability than those derived from the cochlear nerve.[51]

Myrseth et al.[52] was the first to show that vertigo is a strong predictor of reduced quality of life (QOL) in VS patients. Later, several studies have found associations between vestibular symptoms and QOL. Vertigo was associated with a reduction of QOL for VS patients when the two generic questionnaires, Short-Form 36 (SF-36) and Glasgow Benefit Inventory (GBI), were utilized.[52] Other symptoms such as unilateral hearing loss and tinnitus seemed to affect QOL less. Lloyd et al. found that imbalance had a considerable impact on the QOL of patients treated conservatively.[3] In a study by Carlson et al., ongoing dizziness and headache were the strongest predictors of long-term reduction of QOL for patients with VS, while hearing loss, facial nerve function, and tinnitus had less impact on QOL.[53] Vertigo is also suggested to be a predictor of fatigue, which is found to have a negative impact on QOL in VS patients.[36]

8.1.5 Tumor size and growth

The size and growth of vestibular schwannomas can be measured in different ways, with different clinical implications. The tumors tend to have an irregular shape, often with intra- and extra-canalicular components that may affect the brainstem and vestibulocochlear nerve differently. The largest tumor size in the cerebellopontine angle (CPA) on MRI is commonly used as a measure of tumor size when the tumor protracts from inside the internal auditory canal to the CPA.[54] This method was also used at HUS, and for intracanalicular tumors the maximum diameter was measured. Tumor growth has been defined as an increase $\geq$ 2mm.

The Koos grade is often used in literature for classifying VS size based on grade of tumor extension to the CPA, or affection of brain stem. Grade 1: Intracanalicular tumor. Grade 2: Tumor protrudes into the CPA without contact with the brainstem.

Grade 3: Tumor occupies the cerebellopontine cistern without compressing the brainstem. Grade 4: Large tumor with brainstem and cranial nerve compression.[55] Lately, measuring tumor volume has proven to be the most sensitive method of discovering changes in VS size,[56-58] and a 20% volume increase has been used as a cut-off for defining growth. Likewise, volume-doubling time (VDT) is the most sensitive measure of VS growth.[59,60] A review from 2016 found that 33% of tumors grow within three years, and 50% within five years of observation.[61] No reliable predictors of tumor growth were identified. However, two studies in the review found patient-reported imbalance to be associated with tumor growth,[62,63] while a third did not.[8] An objective measure of postural balance has not been studied as a predictor of tumor growth.

8.1.6 Treatment strategies

Treatment options are conservative, with "wait-and-scan", radiation, microsurgery (MS) or a combination thereof. There is no consensus on the choice of initial management, due to a lack of high-level studies comparing the different treatment modalities. However, the significant proportion of non-growing tumors, quality-of-life studies,[64,65] and detection of smaller tumors in the elderly have led to an increase in conservative treatment of VS. Tumor control rate, preservation of cranial nerve function, and maintained quality of life are measures of successful treatment. By and large, from 2001 to 2021 treatment strategies at Haukeland University Hospital (HUS) were based on CPA tumor size (millimeter) and tumor growth, as described by Myrseth et al.[66]:

1. <20 mm, single observation or no growth – Conservative management
2. <20 mm and growth on serial scans – Gamma knife® radiosurgery (GKR) or MS.
3. 20-25 mm, single observation – GKR or MS.
4. >25 mm - MS.

Conservative management with wait-and-scan

Outpatient consultation and contrast axial and coronal thin slice MRI at 6 and 12 months and then annually for ten years. Hearing aid and tinnitus treatment are offered if necessary. Some patients need vestibular rehabilitation due to vertigo or unsteadiness.

Gamma knife® radiosurgery

Gamma knife® radiosurgery is the type of conformal radiation used to treat VS at HUS. All patients are treated with a single fraction, typically 12 Gy delivered to the tumor margin. The goal is to achieve tumor control and maintain cranial nerve function and quality of life. The patients are followed up with annual MRI following GKR.

Microsurgery

Tumors are mainly resected by the retrosigmoid/suboccipital approach at HUS. This approach enables surgery of VS of different sizes, and hearing can be preserved dependent on tumor size and location. Other methods are the translabyrinthine, which destroys the labyrinth, and the middle fossa technique. The latter is most suitable when the tumor is small and located in the inner ear canal, when the aim is to preserve hearing. The approach should depend on the treating centers' experience due to lack of data supporting the superiority of one approach in terms of radical tumor resection and nerve function preservation.[22] Large tumors are typically left with a tumor remnant on the facial nerve to avoid facial nerve palsy. The tumor remnant can be monitored with radiological control and treated upon proven growth or treated up front (if the tumor remnant is voluminous).

8.2 Relevant vestibular anatomy and physiology

This section will review some aspects of vestibular anatomy and physiology that are of particular relevance to describe how a VS can cause vestibular symptoms, the VS' impact on vestibular nerve function, and some background to understand the different

vestibular tests that have been used in this study. The reference list includes some excellent textbooks that cover this field in greater depth.[44,67,68]

A vestibular schwannoma typically arises from the superior or the inferior branch of the vestibular nerve[69,70] (Figure 3), located in the internal auditory canal, with or without extension to the cerebellopontine angle (CPA). A vestibular schwannoma could cause peripheral vestibular loss through compression of the vestibular nerve, due to the VS itself, impaired blood supply to the vestibular nerve, biochemical factors or a combination of these. However, the VS does not necessarily affect all divisions of the vestibular nerve equally, and for this reason, disruption of signals from different sensory receptors may account for some of the difference in vestibular symptoms reported by the patients. The VS' impact on the nerve function has traditionally been investigated by the caloric test, however new methods that are unique in measuring the function of the different vestibular end-organs have been increasingly used, but there has been little comparison of these older and newer methods. The tests are described in section 8.3.

8.2.1 Innervation of the balance organ

Afferent fibers from the lateral and anterior semicircular canals and utriculus constitute the superior vestibular nerve (SVN), while afferent fibers from the posterior semicircular canal and most of the sacculus constitute the inferior vestibular nerve (IVN).[71]

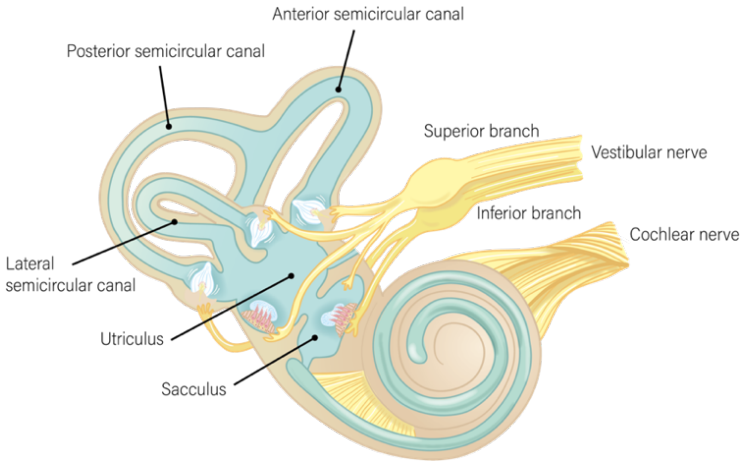

Figure 3. Illustration of the vestibular apparatus by © Jeanette Engqvist – illumedic

Utriculus, sacculus and semicircular canals (SCC)

Utriculus and sacculus are sensitive to gravity and linear accelerations, while the semicircular canals detect rotations.[67,68] This is possible due to their orientation and inertia of mass (Figure 3 and 4). When the head moves, the otoconial layer lags behind, due to mass inertia, and exerts a force against the macula in the otolith organs and against the cupula in the SCC, causing motion-sensitive hair-cells in the macula and cupula to bend. The hair-cells transform a mechanic displacement due to head motion into electric energy. Afferent nerve fibers of the hair-cells show a spontaneous firing rate that increases or decreases depending on the direction in which the otoconial layer moves.[68] The SCC acts so that when one SCC is exited due to for example head rotation, the other SCC in the same plane in the other balance organ is inhibited (push-pull).

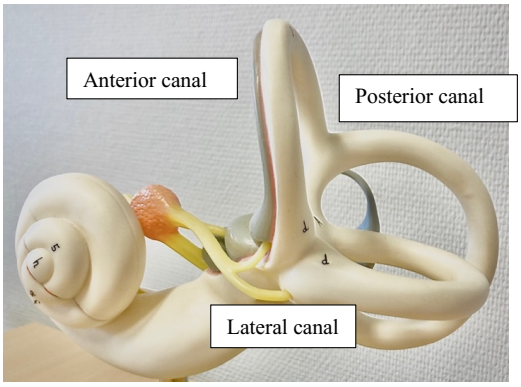

Figure 4. Model of the vestibular apparatus showing orientation of the semicircular canals

The three SCC pairs (Figure 4) that are placed in coplanar planes are:

1) Right and left lateral SCCs.

2) Right anterior and left posterior SCCs.

3) Left anterior and right posterior SCCs.

In addition to the side difference caused by the push-pull manner, an increase of the firing rate in one balance organ will also result in a decrease of the firing rate in the other balance organ, due to commissural inhibitory fibers in the brainstem. Signals from each balance organ will be transferred via the vestibular nerve to the brain, where the signal difference is registered. Together with input from vision and proprioception, the coordination of balance is possible.[67,72]

The vestibulo-ocular reflex (VOR)

The assessment of vestibular function in patients with vestibular schwannoma, as well as most other vestibular disorders, depends to a large degree on measurement of the vestibulo-ocular reflex.[44] Disturbance of this reflex may also account for many of the symptoms, particularly oscillopsia.

The purpose of this reflex is to maintain stable gaze during head motion. The reflex pathway consists of the sensory fibers in the end organs of the semicircular canals, a central processing mechanism, primarily in the vestibular nuclei and cerebellum, and the motor output in the eye muscles (Figure 5).[73] When fixating the gaze, a head turn to the left will, within 8 milliseconds,[74] be followed by an eye movement in the opposite direction that is as fast as the head turn. The reflex leads to stable eyes in space. As this eye movement happen so fast, clear vision will be experienced during head movement.

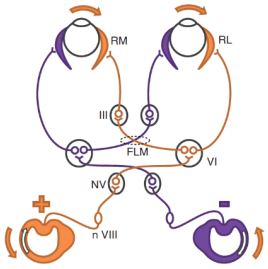

Figure 5. The vestibulo-ocular reflex.
Rotation of the head to the left activates the left lateral semicircular canal and inhibits the right lateral semicircular canal. The signals from the left semicircular canal are transferred via the superior branch of the vestibular nerve to the left vestibular nuclei, cross the brain stem and activate the right abducens nuclei, resulting in contraction of the right lateral rectus muscle and the left medial rectus muscle and thereby movement of the eyes to the right.

Abbreviations: NV: Vestibular nucleus,VI: Abducens nucleus, RL: Musculus rectus lateralis, FLM: Fasciculus longitudinalis medialis, III: Nucleus oculomotor, RM: Musculus rectus medialis

8.2.2 The human postural system

A vestibular schwannoma may cause unsteadiness and postural sway by disrupting peripheral vestibular function, or in the case of larger tumors, through compression of the brainstem or cerebellum, or by general pressure effects due to hydrocephalus.

One purpose of the present study was to examine postural balance in vestibular schwannoma patients using static and dynamic posturography, and a brief review of the human postural system is therefore presented. A more thorough review of this topic may be found in the references[68,75].

The body's ability to maintain balance and a stable perception of our position in relation to the ground relies on the integration of sensory inputs from the vestibular, visual and proprioceptive systems.[44,68,76] Combining information from these three systems helps us to remain stable during various movements.
In addition to being a sensory system, the vestibular system is also a motor system. It sends efferent nerve fibers to the eye muscles, allowing the vestibulo-ocular reflex (VOR), and fibers to the spinal cord via the vestibulospinal reflex that ensures upright position.
In many instances the three systems give the same message. An upright position can be detected by the otoliths, the proprioceptive system, and the vision. If the CNS does

not receive information from one of the systems, the weighting of the two other systems will be regulated upwards, termed sensory reweighting.[75,77,78] The weighting of each of the sensory systems depends partly on the available sensory information. This is important, as information from the sensory systems is not always available or precise. For example, if we are standing on an unstable surface without vision, we have to rely on vestibular information for orientation. The CNS will then down-regulate the unreliable somatosensory information and increase the dependence on vestibular information for postural balance.[79] Peterka et al.[80] showed that for postural orientation, one mainly relies on somatosensory information, and that this shifted to vestibular information when somatosensory information became unreliable due to standing on a moving platform. This implies that under normal conditions, revealing a postural imbalance in patients with a vestibular deficit can be difficult. A balance platform or computer dynamic posturography can measure postural balance objectively. A subtest of the dynamic posturography can disturb visual and proprioceptive input, thereby challenging the vestibular system and revealing slight vestibular deficit. Patients with VS were found to have lower posturography scores then healthy controls.[81]

Loss of unilateral vestibular function and central vestibular compensation

Since vestibular schwannomas are slow-growing tumors, they usually lead to a gradual loss of vestibular function. Vestibular symptoms are usually mild or absent, but some degree of chronic symptoms is not uncommon. A minority of patients report a sudden onset of vertigo similar to the acute vestibular syndrome, or distinct vertigo episodes that may mimic Menière's disease.

Acute damage to the vestibular end-organ or the vestibular nerve can lead to reduced or silenced resting firing frequency on the lesioned side. Via the VOR this asymmetry with the higher firing rate on the healthy side will simulate a permanent rotation to the healthy side and cause the acute phase symptoms of nystagmus slow phase to the lesioned side, rotatory vertigo, nausea, and vomiting.

The static imbalance will normally improve within days or weeks, due to the central restoration of tonic activity on the lesioned side.[72] The secondary neurons located in the vestibular nucleus on the lesioned side will recover their spontaneous firing rate and respond to stimulation of the contralateral labyrinth via the commissural fibers.[68] If the vestibular sensors do not recover, the dynamic changes can be prolonged.[72] When the reduced vestibular function can be measured after three months, it is termed chronic unilateral vestibular loss, and symptoms vary from no dizziness to severe dizziness.[82] The patients often notice that unsteadiness is more prominent when walking in the dark. It is unknown whether vestibular symptoms and the function of the vestibular nerve will change or not during long-term follow-up of VS patients who are treated conservatively, and thus patients with a non-growing tumor. The basis for recovery after unilateral vestibular function loss is the capability for VOR adaptation. Patients with a deficient VOR that can make a covert saccade have less symptoms of the chronic disease.[72] A video head impulse test (vHIT) may be used to examine for a deficient VOR and saccades. When vestibular hair cells becomes fewer due to normal aging, the VOR also compensates.

The connections between vestibular, visual and the proprioceptive system also explain some of the symptoms seen when vestibular dysfunction occurs. The vestibular schwannomas' effect on the vestibular nerve causes less vestibular information to contribute to maintaining postural balance. The information from the proprioceptive system and from vision will therefore be regulated upwards. After an acute vestibular deficit, the information from the vestibular system is impaired and the weighting of the information from vision is regulated upwards. This visual upward regulation is one of the hallmark symptoms of persistent postural-perceptual dizziness (PPPD)[83] that may appear after a vestibular disease, including a VS.

Vestibular rehabilitation

Since neither microsurgery nor radiosurgery can restore peripheral vestibular function, the treatment of vestibular schwannoma patients with significant dizziness or balance problems consists of vestibular rehabilitation.

Vestibular rehabilitation has been shown to be effective in peripheral vestibular diseases.[84,85] The aims of vestibular rehabilitation are reduction of vertigo and dizziness, improving postural control and encouraging a return to previous daily activities.[86] The treatment is tailored for the individual patient. One treatment principle is to repeat exposure to movements that induce vertigo, to achieve central vestibular compensation and decreased symptoms. Adaptation of the vestibulo-ocular-reflex (VOR) is used for patients with unilateral vestibular disease. Head movements when fixating the gaze is one form of treatment: When the VOR is deficient, a retinal slip is induced during head movements. This retinal slip creates an error signal which is used to increase the gain of the vestibular response. Most patients also learn to make a saccade to correct for the deficient VOR.[87] The variation in the time elapsed between the onset of vestibular dysfunction in VS patients and the administration of vHIT may account for parts of the diversity observed in VOR gain and saccades among these individuals.

8.3 Tests of the vestibular apparatus

There is no particular area of the cortex that solely receives vestibular information, as the cortex integrates vestibular, visual, and proprioceptive information. Vestibular function is constructed to function without conscious evaluation of the stimuli, so that testing of the vestibular apparatus has focused on vestibular reflexes. A reflex is an automatic response to a stimulus that does not require conscious effort. The function of the vestibulo-ocular reflex is applied in the caloric test, the video head impulse test (vHIT), and the ocular vestibular evoked myogenic potentials (oVEMP). Similarly, the vestibulo-collic reflex is utilized through the cervical vestibular evoked myogenic potentials (cVEMP). The main intention behind testing the vestibular function is to detect an asymmetry between the two vestibular apparatus, as vestibular symptoms are predominantly due to asymmetric vestibular function.

For many years, the caloric test has been considered the gold standard for detection of vestibular hypofunction. It is limited in that it mainly measures the function of the lateral semicircular canal and thereby the superior division of the vestibular nerve.

Some authors advocate that in many instances the newer and promising vHIT, c-VEMP and o-VEMP tests can replace the caloric test or add information about the vestibular apparatus.[88-91] However, little comparison has been made of these tests.

8.3.1 Vestibular function tests

Caloric test

Caloric test measures the function of mainly the lateral semicircular canal,[92] and hence, indirectly, the superior branch of the vestibular nerve. The test uses a nonphysiologic stimulus (warm and cold water) to evaluate the very low-frequency region ~ 0.003 Hz of the lateral SSC.[82,89] However, the vestibular receptors respond best in a higher frequency range, 0.1 to 3 Hz.[93] The test is easy to perform and the interpretation is relatively straightforward. It is suitable for detecting both unilateral and bilateral vestibular loss. It can detect a unilateral vestibular loss or canal paresis ranging from 26 to 100% based on comparison of the two ears (by Jongkees' formula). The test's sensitivity to detect a hypofunction in a VS patient depends on the tumor size and ranges from 62-95%.[94-98]

The caloric test may cause the patient discomfort such as nausea and is contraindicated if there is a tympanic membrane perforation or recent ear surgery. It may also not be suitable for young children.

The peak velocity of the induced slow phase nystagmus is used in Jongkees' formula[99] to calculate percentage response difference between the two ears:

$$\frac{(RW + RC) - (LW + LC)}{(RW + RC) + (LW + LC)}\ x\ 100$$

Where RW=Right warm, RC= right cold, LW= left warm, LC= left cold.

In most laboratories a response asymmetry above 20-25% is characterized as unilateral weakness, which corresponds to two standard deviation values above the mean.

Video head impulse test (vHIT)

vHIT can be used to measure the function of each of the six semicircular canals individually, and thereby both the superior and inferior part of the vestibular nerve. This is performed by comparing the velocity gain of the vestibulo-ocular reflex (VOR) elicited by each canal, with established normative values: and additionally, by detecting abnormal catch-up saccades.

The test uses a high-frequency (2.5 Hz), high-acceleration, physiologic stimulus.[82] The sensitivity for vHIT to detect vestibulopathy in a VS patient diverges in the literature (31-90%),[98] and in some studies sensitivities are found to be associated with tumor size.[94,96,97,100] The probability of a pathologic vHIT generally increases with increasing unilateral weakness of caloric examination.[94,101] vHIT can detect mild impairment of canal function[102] and VOR gain is largely unaffected with age.[103] The test is generally well-tolerated, even by children.[104]

Gain is often calculated as the ratio of the area under the eye velocity curve in relation to the area under the head velocity curve, during the head impulse. Patients with a unilateral vestibular deficiency have a reduced VOR gain during head turn to their affected ear (usually less than 0.7), and to correct for the reduced gain they make catch-up saccades.[74] Catch-up saccades that occur during the head impulse are termed covert, and overt if they occur after the head impulse. The significance of the catch-up saccades is currently being investigated more thoroughly. Studies have proposed that including repeatable catch-up saccades as a sign of pathologic vHIT, despite normal gain value, increases the sensitivity of vHIT.[105] Catch-up saccades as a measure of vestibular plasticity have also been investigated.[106] Batuecas-Caletrio found that patients with disorganized saccades correlated with worse clinical outcomes, as measured by the Dizziness Handicap Inventory.[107] However, methods for calculation of VOR gain and saccades are yet not standardized. There are some pitfalls to be aware of regarding vHIT performance[74] and interpretation of results. It can be challenging to separate an artefact from a pathologic result.[108] Also, some patients with unilateral weakness may have compensatory saccades for head impulses to the *healthy* side.[97] This is explained by the lack of disinhibition from the lesioned side, with the result of a too small compensatory eye movement response.[74]

Vestibular evoked myogenic potentials (VEMP)

VEMPs are unique as they may be used to assess the function of each of the four otolith organs individually. They can also be used to test the function of the two divisions of the vestibular nerve. This is done by repeated stimulation of the otolithic macula with sound or vibration, which produces short latency surface potentials that can be measured.[109] The tests are generally well-tolerated and may also be used for young children.[110]

Cervical vestibular evoked myogenic potentials (cVEMP)

cVEMP provides information about sacculus function and thereby the inferior vestibular nerve. The prevalence of vestibulopathy found by cVEMP in a VS patient is reported to be 50-79%.[95,98,111] The sacculo-collic response is a reflexive adjustment of the musculature in the neck triggered by activation of the saccule. Any lesions along the cVEMP reflex pathway may cause abnormal test results.[112] cVEMP is characterized by a biphasic waveform that starts with a positive wave and is followed by a negative wave (Figure 11). The latency from the click stimulus to the peak of the positive wave is 13 msec, and this point on the wave is termed P1 or P13. The latency to the peak of the negative wave follows after 23 msec and is referred to as N1 or N23.[27] The amplitude of the response is quantified in microvolts between P1 and N1. The response is inhibitory.[112]

The literature consistently describes a decrease in cVEMP amplitude, decreased EMG amplitude and higher thresholds with increasing age.[113,114] Studies of healthy controls have shown a decreased cVEMP response rate at age > 60 years.[115]

In the results of Piker et al.[116] they suggest increasing tone burst to 750 or 1000 Hz when a VEMP responses is absent at 500 Hz. The result of the test is often given as % side-to-side difference in amplitude (formula in method section) and response /no response, depending on whether the response can be measured and reproduced. A significantly reduced response[111] or an absence of response indicates a loss of function. A conductive hearing impairment reduces the reflex response and vibratory or mechanical stimulation must be used instead.[112]

Ocular vestibular evoked myogenic potentials (oVEMP)

oVEMP measures the function of the utricle, and thereby the superior part of the vestibular nerve. The prevalence of vestibulopathy found by oVEMP in a VS patient is reported to be 50-73%.[90,98,111] oVEMP is characterized by a negative peak 11 msec after stimulus, referred to as N1 or N11, followed by a positive peak 15 msec after stimulus, referred to as P1 or P15 (Figure 12). To elicit the reflex one can use sound or direct vibration of the skull with e.g. a Bruel & Kjaer 4810 Mini-Shaker. Any stimulus that produces translation of the otoliths can be utilized. The reflex response is measured from the extra-ocular muscles by surface electrodes placed near the eyes. In the case of a vibration stimulus, a conductive hearing loss will not reduce the response. Rosengren et al. investigated the age effect on oVEMP response, and the oVEMP elicited by taps and vibration did not demonstrate age effects.[117] Evaluation of test result is similar to that described for cVEMP.

8.3.2 Test of postural control

Pathologies affecting the vestibular, visual, and proprioceptive system may affect postural control. A significant proportion of VS patients feel unsteady. Posturography is a clinical test to quantify postural control while upright, and can be performed in a static or dynamic manner, termed static and dynamic posturopraphy. Dynamic posturography was developed to increase the sensitivity and specificity of the easier static posturography. Yet, there is no appropriate posturography test available with good enough sensitivity and specificity for the diagnosis of balance disorders.[118] However, together with other vestibular tests thus can give additional clues concerning the suspected vestibular disorder, an objective measure of balance and a quantitative measure of balance before and after rehabilitation.

Static posturography

Postural control is quantified by standing on a force platform with eyes open and eyes closed. The center of pressure (COP) under the feet moves according to the forces used to attempt standing upright. The length of COP movement on the platform measured in mm, termed the path length, can be used to quantify postural control. In a study by Goplen et al., abnormal sway was defined as path length ≥ 1600 mm with eyes closed. The cutoff for abnormal result was based on path length > 95% in a control group.[119] In a study by Berge et al.[120] unsteadiness measured by static posturography was found to be an independent predictor of mortality in patients evaluated for dizziness with suspected vestibular origin.

Figure 6. Static posturography

Dynamic posturography

The term computerized dynamic posturography means that a computer controls the platform movement.[118] A widely used test of postural balance is the Sensory Organization Test (SOT). This system can manipulate the proprioceptive and visual inputs and objectively quantify their respective contributions in maintaining balance,[118] due to the six combinations of stable or movable platform, movable visual surround, eyes closed or a fixed visual surround. The movement of platform and visual surround are sway-referenced, a technique used to disturb the proprioceptive and visual input.

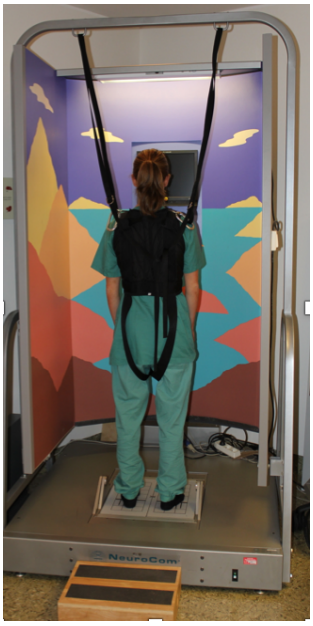

Figure 7. Dynamic posturography

9. AIMS OF THIS THESIS

9.1 Overall aim

The overall aim of this thesis was to study how vestibular symptoms and vestibular function are affected by untreated vestibular schwannoma, in a short- and long-term perspective. This has implications for patient examination, counselling, treatment, and follow-up.

9.2 Specific aims

Study 1

The aim of this study was to find out whether vertigo is associated with known objective parameters such as tumor size, location, vestibular function, hearing, and postural stability in patients with untreated VS.

Study 2

In this study the aim was to study the development of dizziness, objective postural sway, and caloric function during long-term observation of untreated VS patients without growth of tumor.

Study 3

The aim of this study was to predict whether postural sway is associated with tumor growth within three years' observation of VS patients initially elected for conservative management.

Study 4

The aim of the study was to assess vestibular function with the newer tests; cervical- and ocular vestibular evoked myogenic potentials (c-and oVEMP) and the 6-canal video head impulse test (6-canal vHIT) in addition to the established caloric test. The

aims were to compare the tests' prevalence of abnormal results for the tumor side and the non-tumor side in untreated VS patients, and relate the results to tumor volume.

10. MATERIALS AND METHODS

10.1 Ethics

The studies were approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK114/01, REK 2015/2331 and REK Sør-Øst 2017/765). For study 4, all patients gave their written informed consent on inclusion and for study 1-3, informed consent to collect and analyze data was obtained from all patients when enrolled. The database for studies 1-3 and its use for scientific studies were approved by the Norwegian National Data Inspectorate (NSD 13199).

10.2 Design

Studies 1 and 4 were cross-sectional observation studies on subjects from a prospectively maintained database. Studies 2 and 3 were longitudinal observation cohort studies. The literature review for this thesis was completed on November 1, 2022.

10.3 Subjects

All patients were referred to Haukeland University Hospital.

Part 1 of the PhD project (studies 1-3, Figure 8)
433 newly diagnosed untreated vestibular schwannoma patients were compiled in a database in the period 2001-2010 (figure 8) and were included in study 1. The patients were followed up at regular intervals (6 months and 1, 2, 5, and 10 years). Out of these 433 patients, 114 patients did not require treatment during follow-up (by August 2018), and were included in study 2. Inclusion criteria were MRI and either caloric tests or clinical data at two time points with at least one year's observation. 204 of the 433 patients were assigned to initial wait-and-scan management and included in study 3. Patients with bilateral VS or suboptimal MRI quality were excluded.

Part 2 of the PhD project (study 4, Figure 8)

Patients with newly diagnosed untreated VS were enrolled at HUS in the period June 2017-June 2019. Inclusion criteria were patients assigned to an annual wait-and-scan protocol with small- to medium-sized tumors (< 25 mm) and completion of the vestibular tests consisting of air-conducted cVEMP, bone- conducted oVEMP, bithermal caloric test, and 6-canal vHIT. Exclusion criteria were bilateral VS and intracochlear VS.

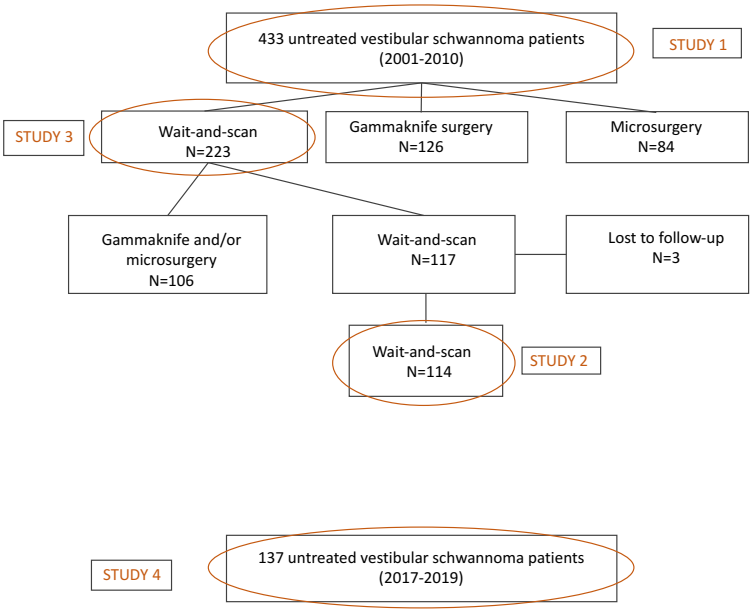

Figure 8. Overview of the studies in the PhD project and from which database they originate. The flow diagram shows treatment of 433 vestibular schwannoma patients as of August 2018.

10.4 Vestibular function tests

10.4.1 Caloric test

The bithermal caloric test was performed by 30 seconds' irrigation of warm (44°C) and cold (30°C) water in each ear canal. Videonystagmography (Hortmann, Germany was used until 2012, and Interacoustics after 2012) was used to record slow phase nystagmus velocities. The Jongkees formula[99] was used to calculate the response difference in the right and left ears, and a unilateral weakness > 25% was defined as canal paresis. From June 2003, caloric testing was included in the testing protocol.

10.4.2 Video head impulse test (vHIT)

Function of the lateral, posterior, and anterior semicircular canals was measured with an ICS Impulse device (Otometrics, Natus Medical, Pleasanton CA, USA) that assesses the gain of the vestibulo-ocular reflex (VOR) and show 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. While the patients were instructed to fixate the gaze on a stationary dot on the wall 1-1.2 m in front, approximately 10 rapid head impulses of around 10-20 degrees were randomly delivered in the plane of each semicircular canal. Attention was paid to not touch the goggles during testing.

Figure 9. Performance of vHIT at Haukeland University Hospital. Picture: Thor Ellingsen/Skorpa Nilsen.

The mean VOR gain for each semicircular canal was measured automatically 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 was considered abnormal for the horizontal head impulses, and a mean gain < 0.7 was abnormal for the vertical head impulses. Four authors (FG, JB, KN

and SN), blinded to tumor locations 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 within the group. Corrective saccades with a velocity of ≥ 50 degrees/second occurring in ≥ 80% of head impulses were considered abnormal.[105,121]

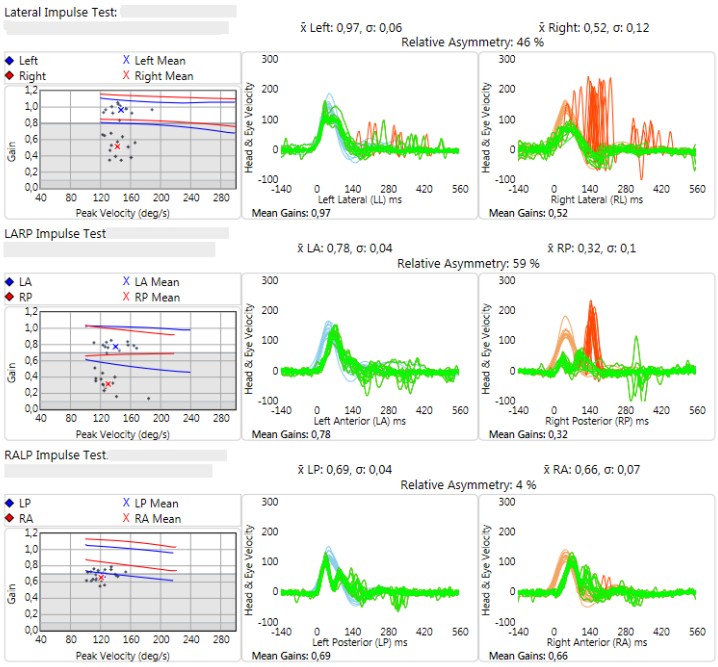

Figure 10. Normal vHIT results of left side semicircular canals and pathologic vHIT results of right lateral and right posterior semicircular canals.

10.4.3 Cervical and ocular vestibular evoked myogenic potentials (cVEMP and oVEMP)

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

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

cVEMP

Patients were seated and instructed to turn their heads to one side to contract the sternocleidomastoid muscle on the opposite side (Figure 10). Air-conducted tone bursts were delivered to the ear ipsilateral to the contracted muscle with a frequency of 500 Hz and a stimulus intensity of 100 dB normal hearing level. During the test, the patients received feedback from an electromyography (EMG) display that showed a green/red bar when the appropriate muscle tone was within target range. To compensate for unequal muscle contraction on the right and left sides, EMG weighting was used. An asymmetry ratio ≥0.3 was considered abnormal.[111,121]

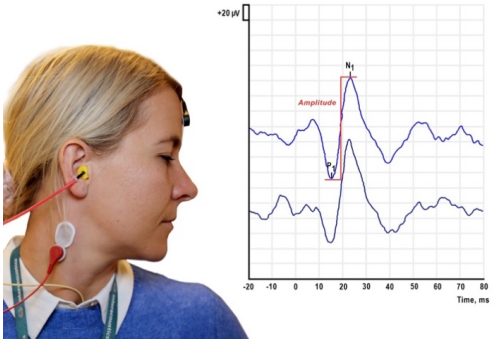

Figure 11. cVEMP electrode setup and surface waveforms performed at Haukeland University Hospital.
Illustration: Thor Ellingsen/Skorpa Nilsen.

oVEMP

Bone-conducted stimuli, "minitaps", using a handheld mini-shaker (Brüel & Kjaer, type 4810, Naerum, Denmark) 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 upwards. The

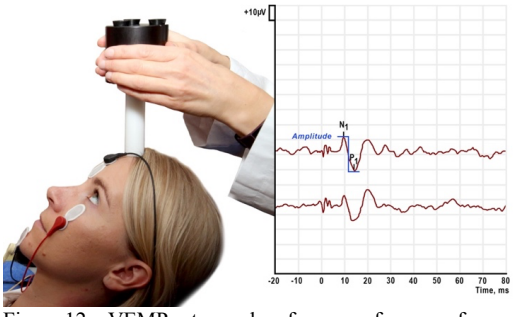

Figure 12. oVEMP setup and surface waveforms performed at Haukeland University Hospital
Illustration: Thor Ellingsen/Skorpa Nilsen.

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.[111,121]

10.5 *Posturography*

Static posturography was performed for patients included before 2006, and dynamic posturography was performed for patients included after 2006. The same type of posturography was used for baseline and follow-up in each patient.

Static posturography was carried out using a force platform (Cosmogamma, Bologna, Italy) containing three pressure transducers. The movement of the center of pressure was measured, while the patient was instructed to stand quietly for one minute with eyes open and one minute with eyes closed. The path length measured with eyes closed was used for statistical analysis. Based on a previously published study with normative data from healthy individuals with a mean age of 52 years, a path length ≥ 1,600 mm defined the patient as unsteady.[119,124]

Dynamic posturography (EquiTest, NeuroCom, USA) and the Sensory Organization Test (SOT) protocol measure postural sway under six different sensory conditions. Condition 1 (SOT1): visual surround stable, eyes open, platform stable. Condition 2 (SOT2): visual surround stable, eyes closed, platform stable. Condition 3 (SOT3): visual surround moves, eyes open, platform stable. Condition 4 (SOT4): visual surround stable, eyes open, platform moves. Condition 5 (SOT5): visual surround stable, eyes closed, platform moves. Condition 6 (SOT6): visual surround moves, eyes open, platform moves. The composite score was calculated by independently averaging the equilibrium scores for conditions 1 and 2, adding these two scores to the equilibrium scores from each trial of sensory conditions 3, 4, 5, and 6, and dividing the sum by 14. Missing trials for conditions 3, 4, 5, and 6 were replaced by the average equilibrium score for that condition. Unsteadiness was defined as a composite score lower than the normative values supplied by the producer.[122-124]

10.6 Audiometry

Hearing was measured using bilateral pure-tone air-conducted audiometry and monosyllable speech discrimination (SD). The pure-tone average (PTA) was the arithmetic mean of the frequencies of 0.5, 1, 2, and 3 kHz, as required by Otology & Neurotology at the time of publication.[122]

10.7 Questionnaires

10.7.1 Dizziness symptoms questionnaires

Dizziness symptoms quantified on a VAS scale

The patients were asked to quantify their dizziness on a 100-mm visual analog scale (VAS) ("How troublesome is your dizziness usually?"). To make interpretation of the VAS scores more intuitive, we used a grading system and cut points developed for pain.[125] A VAS score of 0 to 4 mm was classified as "no dizziness", a score of 5 to 44 mm was classified as "mild dizziness", a score of 45 to 74 mm was classified as "moderate dizziness", and a score of 75 to 100 mm was classified as "severe dizziness".[122]

Dizziness time course and characteristics:

The patients were asked about the time course of their dizziness (attacks, periods, constant or no dizziness) and the characteristics of dizziness (spinning, rocking, walking on pillows, and other characteristics) during the last three months.[123]
The interviewing physician filled in a questionnaire, including question as to whether or not the patients had complained of dizziness or imbalance.

10.8 Measurement of tumor size

10.8.1 Measurement of tumor size in studies 1 and 2:

The tumors were measured in three planes on MRI (T1, contrast axial and coronal MRI). Tumor location was classified as extrameatal or intrameatal, depending on

whether or not the tumor extended into the CPA. In predominantly extrameatal tumors, the intracanalicular component was not included in this measure.[122] In study 1, tumor size was defined as the largest diameter in the CPA. Study 1 included a wider range of tumor sizes compared to the other studies.
In study 2, tumor volume (V) was calculated using the formula $V = 0.4\ x\ l\ x\ w\ x\ h$ Tumor diameters along the pyramid (l) and at horizontal (w) and vertical (h) orthogonal angles were measured.[126]

10.8.2 Measurement of tumor size in studies 3 and 4

The diagnostic MRI, and for study 3 also the routine three-year follow-up scan, were reviewed for each patient. For patients in study 3 who received interventional treatment within three years, the pretreatment MRI was obtained. Preferably T1-weighted MRI with gadolinium contrast was selected. If not available, CISS or T2-weighted MRI sequences were analyzed. Volumetry was performed on iPlan Brainlab Elements (Version 2.4.0 for study 3 and version 3.3 for study 4, Brainlab AG, Munich, Germany). We used the Smartbrush function, which provides an instant method for outlining the tumor on each image slice (Figure 13). A software algorithm reconstructed a three-dimensional object based on the selected areas and presented a detailed report, including object volume in cubic centimeters (cm3). For 38 patiens in study 3, volumetric measurements on Brainlab were not possible, due to old MRI format. For these patients, the volume was calculated using the following formula:[124]

$$V = \frac{4}{3}r^3 = \frac{4}{3}\left(\frac{x}{2}\right)\left(\frac{y}{2}\right)\left(\frac{z}{2}\right) = \frac{xyz}{6}$$

In study 4, Koos classification[55] of the tumors was also conducted, together with the registration of the largest diameter on axial MRI.

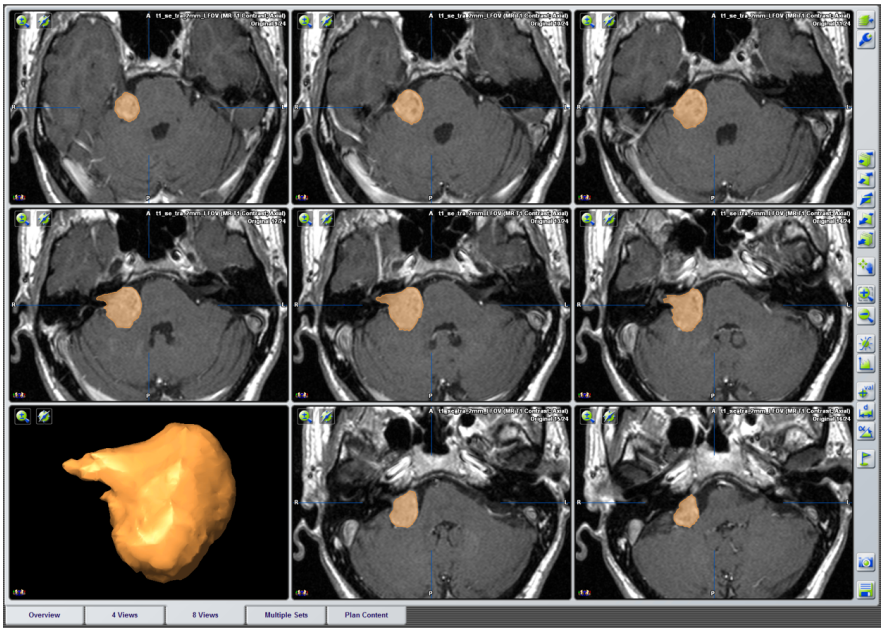

Figure 13. Volumetry on iPlan Brainlab Elements.
The Smartbrush function provides an interactive method for 3D object creation by outlining an area on each image slice.[124]

10.8.3 Growth analysis in study 3

In accordance with recent studies, an increase in tumor volume ≥ 20% was considered to represent significant growth outside the margin of error.[56,57,127,128] Volume-doubling time (VDT) was calculated using the following formula:

$$VDT = \frac{ln2(t2-t1)}{\ln\left(\frac{V2}{V1}\right)}$$

The VDT describes growth in terms of an exponential model.[59,60,129] A VDT that tends towards positive or negative infinity implies a stationary tumor, while a VDT close to zero implies a tumor that is growing or shrinking rapidly. For statistical analysis, we therefore instead used the reciprocal value, denoted as VDT^{-1} (number of doublings per year). VDT^{-1} increases with growth rate, and a negative VDT^{-1} implies tumor shrinkage, thereby facilitating conventional statistical analysis.[124]

10.9 Statistical methods

Continuous variables were presented with means and standard deviation (SD), or medians and interquartile range (IQR). Continuous variables were compared between groups by independent sample t-tests in the case of normally distributed variables, or Mann-Whitney U-tests for non-normally distributed variables. Categorical variables were reported with counts and percentages and were compared between groups by Pearson's chi-squared test.

For paired data, McNemar's test for paired data (chi-square and exact p-values) was used to compare categorical variables at baseline with data from the last clinical control. Paired t-tests were used to compare continuous variables at baseline with data from the last clinical control.

Univariate and multivariate logistic and linear regression analyses were performed with stepwise backward-selection estimation based on a significance level of p greater than or equal to 0.2 (study 1), or 0.1 (study 3), as the removal criterion from the multivariate model. Regression analyses were used to assess relationship with outcome and predictor variables in studies 1, 3 and 4.

Two-sided p-values less than 0.05 were considered statistically significant. Statistical analysis was performed with STATA software (StataCorp, USA).

11. SUMMARY OF MAIN RESULTS

11.1 Summary of the results of study 1

We included 433 patients with untreated VS. The mean age was 56 years (range 16-84 years) and 53% were women.

Dizziness

35% of the patients reported no dizziness on a 100-mm visual analog scale in response to the question "How troublesome is your dizziness usually?" Severe dizziness was reported by 9%, moderate dizziness was reported by 22% and mild dizziness was reported by 34%.

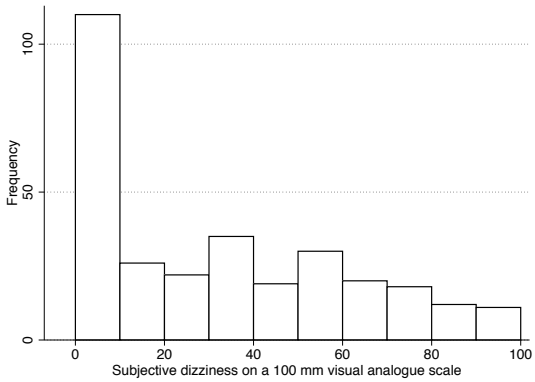

Figure 14.[122] Dizziness severity in 303 patients with untreated vestibular schwannomas. Patient responses to the question "How troublesome is your dizziness usually?" on a 100-mm visual analog scale.

Canal paresis

Canal paresis was found in 72% of the patients. Patients with larger tumors had an odds ratio for canal paresis of 1.16 ($p<0.0005$). The relationship between tumor size and canal paresis is shown in Figure 15.

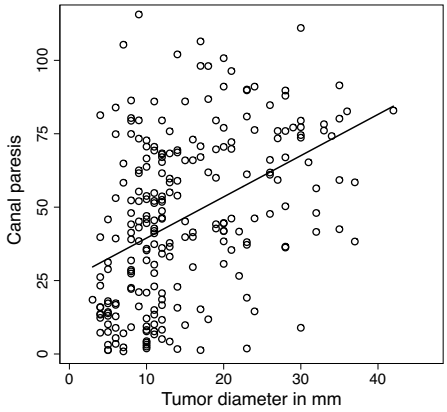

Figure 15.[122] Scatterplot showing the relationship between tumor size and canal paresis. Tumor size was defined as the largest tumor diameter in millimeters on MRI.

Predictors of vertigo

Dizziness was associated with impaired vestibular function and postural instability. Patients with canal paresis had an odds ratio of 3.43 for being dizzy (p=0.006). In the case of postural instability the odds ratio for being dizzy was 3.94 (p=0.001). Tumors > 20 mm were possibly associated with less dizziness (p=0.07). There was no association between dizziness and age, gender, intrameatal tumor location, hearing level or speech discrimination.

11.2 Summary of the results of study 2

114 patients out of the initial 433 untreated VS patients remained untreated by August 2018 and were included in study 2 (Figure 8). At baseline, moderate to severe dizziness was reported by 27%, canal paresis in 51% and postural unsteadiness in 17% of the patients. We found no significant change in the proportions of patients with moderate to severe dizziness, postural unsteadiness or canal paresis from

baseline to follow-up after 3, 9 and 9 years, respectively (Figure 16). The median radiologic follow-up time was 10 years.

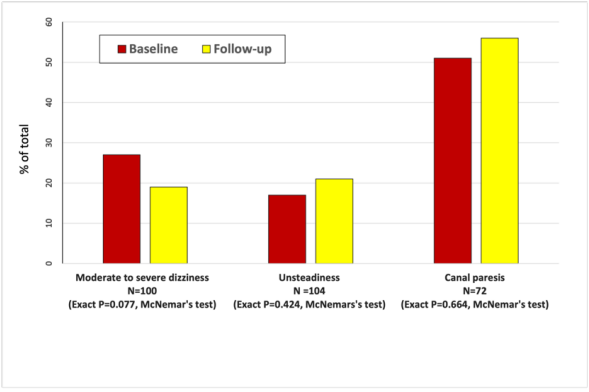

Figure 16.[123] Proportions with moderate to severe dizziness, unsteadiness and canal paresis at baseline and follow-up.

11.3 Summary of the results of study 3

From the initial 433 VS patients, 204 were selected for conservative management and included in the study (Figure 8). 26% of the patients were classified as unsteady measured by posturography. Tumor growth within three years of observation occurred in 51% of the patients. Unsteady patients had an odds ratio of 5.6 (95% CI 2.6, 11.8) for growth compared to the steady patients (Table 1).

Logistic regression analysis of baseline predictors of tumor growth (relative growth >20%)

Variable	Observations	Odds ratio	95% CI	p Value
Univariable				
Age interval (y)	204			
<50.5 (reference category)				
50.5-57.0		0.85	0.39, 1.86	0.691
57.1-63.7		0.92	0.42, 2.02	0.842
>63.7		0.49	0.22, 1.08	0.076
Sex (female)	204	0.75	0.43, 1.31	0.310
Unsteady (posturography)	204	4.77	2.32, 9.81	<0.001*
Unsteady (history)	204	1.80	1.00, 3.21	0.048*
Tumor size (cm^3)	204	0.82	0.57, 1.18	0.290
Hearing level (PTA)	200	1.00	0.99, 1.01	0.520
Canal paresis > 25%	133	1.95	0.97, 3.95	0.061
Dizzy (history)	203	1.72	0.99, 3.01	0.056
Tinnitus (history)	203	1.58	0.84, 2.98	0.160
Multivariable				
Unsteady (posturography)	204	5.56	2.62, 11.80	<0.001*
Age interval (y)	204			
<50.5 (reference category)				
50.5-57.0		0.87	0.38, 1.97	0.732
57.1-63.7		0.98	0.43, 2.22	0.953
>63.7		0.38	0.16, 0.90	0.028*

* $p < 0.05$

CI = confidence interval, PTA = pure-tone average, y = years

Table 1.[124] Logistic regression analysis of baseline predictors of tumor growth (relative growth > 20%).

Significant growth (>20% volume increase) was found in 77 % of the unsteady patients and in 42% of the steady patients (p<0.001) (Figure 17).

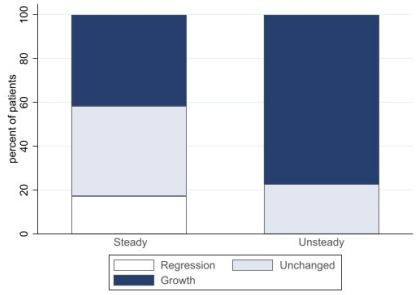

Figure 17.[124] Proportion of significant growth and regression in steady and unsteady patients.

11.4 Summary of the results of study 4

In this cross-sectional study, 137 patients with untreated small to medium-sized vestibular schwannoma were included. The mean age was 55 years (range 28-78 years). The median tumor volume was 0.26 cm^3 and the mean tumor size (maximum diameter) was 10.5 mm. The main findings were sensitivity of caloric test, 6-canal vHIT, cVEMP and oVEMP (Table 2). Caloric test was abnormal on the tumor side in 47% of the patients and in 2% on the non-tumor side, while 6-canal vHIT was abnormal on the tumor side in 51% of the patients and in 23% on both sides or on the non-tumor side. Combining cVEMP with caloric test increased the sensitivity to 65%, while 6% had abnormal results on both sides or the non-tumor side.

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

Abbreviations: vHIT: video head impulse test; cVEMP: cervical vestibular evoked myogenic potentials; oVEMP: ocular vestibular evoked myogenic potentials

† Sensitivity defined as abnormal result on tumor side or both sides

*Abnormal vHIT in at least one semicircular canal.

** Bilateral absent VEMP responses defined as normal

Table 2.[121] Prevalence of abnormal test results related to tumor side in 137 patients with untreated vestibular schwannoma.

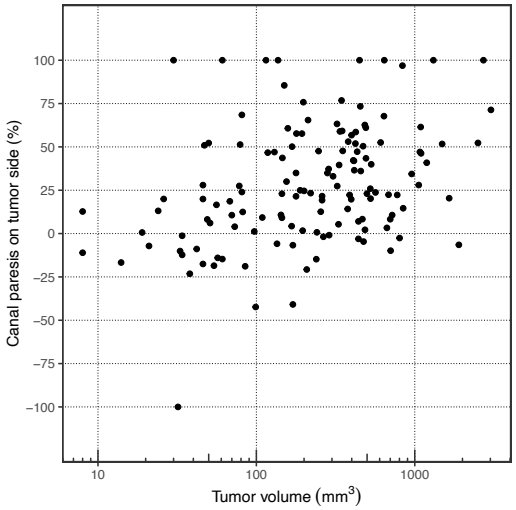

Figure 18.[121] Scatterplot showing the relationship between caloric asymmetry on the tumor side (%) and markings of tumor volume (mm^3) on a logarithmic scale.

Associations with vestibular test results and tumor volume

Unadjusted linear regression analyses showed a significant relationship between canal paresis on the tumor side and tumor volume (cm^3) (coeff. 20, $p = 0.001$). Gains of LSC, PSC, and ASC were related to tumor volume (coeff. -0.08 and $p = 0.012$, coeff. -0.09 and $p = 0.016$, coeff. -0.06 and $p = 0.03$), respectively. On performing unadjusted logistic regression analyses, 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.

12. DISCUSSION

In this thesis we have described the vestibular symptoms, postural balance, and vestibular function both at baseline and on follow-up in patients with untreated vestibular schwannoma. The untreated VS patients were included with the purpose of describing the natural course of the disease. The tumors were mainly small to medium-sized and our results suggest that tumor size is associated with vestibular function.

We found that only a minority of VS patients report severe dizziness, and one third report no dizziness. Dizziness was associated with canal paresis and postural instability. Long-term observation of VS patients without growth of tumor showed no deterioration of dizziness, unsteadiness or canal paresis. Observation of patients who were selected for conservative management showed that 51% of the patients had tumor growth within three years, and patients with postural unsteadiness had increased odds for tumor growth compared to the steady patients. Comparing vestibular tests, caloric test and the 6-canal vHIT had the highest sensitivity for detecting vestibular schwannomas. vHIT was limited, with a high prevalence of abnormal results also on the non-tumor side. The combination of caloric test and cVEMP resulted in a relatively high sensitivity and a low prevalence of abnormal results on the non-tumor side. The prevalence of canal paresis at baseline varied in the different study populations, from 72% in study 1 to 47% in study 4. Study 1 included patients with larger tumors compared to the other studies, which included subgroups from the population in study 1. Canal paresis and 3-canal vHIT gain were found to be volume dependent.

12.1 Vestibular symptoms

Our main findings in study 1 were that patients with VS often have dizziness, although only 9% report severe dizziness and about 30% report no dizziness, as shown in Figure 14. The reason for this diversity in dizziness symptoms is not known

and in our study we can only explain a small part of this variation; dizziness is associated with canal paresis and postural instability. Patients with canal paresis had increased odds for being dizzy compared to patients with normal caloric function. Postural instability, measured by posturography, was also associated with dizziness. More surprisingly, there was no relationship between dizziness and tumor size. To the best of our knowledge, this is the first study to analyze objective factors as predictors of subjective dizziness in untreated VS patients. When informing a VS patient about vestibular symptoms caused by a VS, it is important to underline that even if some dizziness is common, only a few have severe dizziness and many are not dizzy at all. These patients with severe dizziness should also be assessed for other diseases that may cause dizziness, as persistent postural-perceptual dizziness (PPPD) that can often be treated with vestibular rehabilitation.

The results of study 2 suggest a good long-term prognosis regarding vertigo in untreated VS patients, as there was no significant change in dizziness from baseline and after three years of follow-up. These results are in accordance with Breivik et al.,[50] who found no significant change in vertigo VAS from baseline to follow-up. In the study by Godefroy et al.,[130] 41 VS patients were observed for vertigo for 47 months. Some of the patients' vertigo improved, while some experienced an exacerbation, but no trend was reported.

12.2 Vestibular functions and postural balance

Canal paresis at baseline and follow-up

The prevalence of canal paresis varies in the different populations covered by this thesis. One important finding is that 72% of the patients in study 1 already have canal paresis when they are diagnosed with a VS. Furthermore, canal paresis was associated with increasing tumor size and the different tumor sizes probably explain some of the variations in the different patient populations in our studies. In the subgroup of VS patients who underwent conservative management and were followed over time, thus had a non-growing tumor, 51% of the patients had canal paresis at baseline. This did not change significantly when tumor was observed for a

mean of nine years. A significant proportion of patients with canal paresis is also demonstrated in the literature. Humphriss et al. found that 63% of the VS patients had canal paresis,[131] and in a group of VS patients selected for surgery, 86% had canal paresis, defined as unilateral weakness > 20 %.[132] These findings indicate that canal paresis often occurs while the tumor is relatively small. The unchanged function of the caloric test during observation of tumor is in contrast to the deterioration of hearing seen in the same group.[45,49,50]

Caloric test, vHIT, cVEMP and oVEMP at baseline

We found that none of the tests had high sensitivity to detect a vestibular schwannoma. Even when performing all these vestibular tests, 21% still had normal vestibular function on the tumor side, so that vestibular tests are not suitable for VS screening. The 6-canal vHIT and caloric tests were the most sensitive tests and approximately equally sensitive. However, it is also important to report the test result on the non-tumor side when considering a test's sensitivity. For some tests we often also found abnormal results on the non-tumor side, which makes the interpretation of the tests more difficult. vHIT, and particularly the posterior canal, was often abnormal on the non-tumor side and thereby limited in identifying the side of lesion. This is probably due to the tumor affecting the non-tumor side[74] and the test method. cVEMP was more sensitive than oVEMP and both tests had a low prevalence of abnormal tests on the non-tumor side. That fact that caloric test, cVEMP and oVEMP were defined as abnormal based on asymmetry, and vHIT was not, may possibly explain some of the higher prevalence of abnormal results on the non-tumor side in vHIT. Only a few studies have also evaluated the results on the non-tumor side. Lee et al.[133] reported vHIT VOR impairment on the tumor side in 80%, on the non-tumor side in 43% and on both sides in 42%. Absent VEMP responses were reported for both sides, and asymmetry ratios were not used.

Around 10% of the patients showed a bilateral lack of VEMP response and these were categorized as normal. In a study by Berge et al.,[134] an increased hearing threshold in the best hearing ear predicted reduced postural balance. There might

possibly be some common age-related changes in the cochlea and the otholith organs affecting the balance.

Performing cVEMP together with a caloric test resulted in a relatively high sensitivity and a low prevalence of abnormal results on the non-tumor side, which was thus appropriate to detect vestibulopathy in the superior and inferior nerves. On evaluating vestibulopathy in this patient group, these tests seem to give most information.

In this study we found that when a caloric test is performed, adding vHIT of the lateral canal does not provide additional information. However, adding a caloric test to lateral canal vHIT increased the sensitivity. Generally, adding more tests increased the sensitivity, but also the prevalence of abnormal results on the non-tumor side (Table 2). The tests also overlap to some degree and this is probably due to the tumor affecting a varying amount of nerve fibers from the vestibular end organs. The difference in sensitivity between the caloric test and the lateral canal vHIT, which both test the lateral canal, could be due to the testing at low frequency in the caloric test and high frequency in vHIT.

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. It is therefore difficult to compare the sensitivities of the tests in relation to each other.
The sensitivities of the different tests are reported to be 62 to 72% for caloric test,[94,96 97,100,122] 27 to 90% for lateral canal vHIT,[94, 96-98,100,111,133,135,136] 50 to 73% for oVEMP[95,98,111] and 50 to 79% for cVEMP.[90,95,111] Sensitivities of the anterior canal vHIT are reported to be lower than for the lateral and posterior canal.[111,135,136] Generally, we found lower sensitivities, and this could be due to the smaller tumor size in our study. That we found an association between tumor volume and sensitivity of caloric test and vHIT, correspond with previous findings.[96,97,122] We found no association between VEMP asymmetry and tumor volume. However, some studies have shown this relationship.[95,111]

Postural unsteadiness measured with posturography at baseline and follow-up

One of the main findings in the thesis is the unchanged prevalence of unsteadiness in patients selected for conservative management when observed for nine years. The prevalence of unsteady patients in this thesis varied in different populations, with 17% in study 2 and 26% in study 3, which is less than reported in the literature. In the study from Collins et al.[137] 49% had abnormal path lengths with eyes shut before VS surgery. Gerosa et al.[138] found abnormal results for dynamic posturography in 62% of a VS group before treatment with GKR. Indications for such treatment can be large tumors, growing tumors and symptoms such as unsteadiness and dizziness. Theoretically, nervousness before treatment may also cause more unsteadiness on the platform.

With the findings of a stable postural balance in a non-growing tumor and the reporting in the literature of an increased prevalence of unsteadiness in larger tumors, we could hypothesize that a growing tumor leads to more unsteadiness. As mentioned in the early history of VS, the theory of a lack of imbalance and a slowly growing tumor was already suggested at that time.

12.3 Tumor size, growth, and treatment

12.3.1 Tumor size and vestibular tests

As shown in Figure 15, we can see that the patients with the smallest tumors rarely have canal paresis, and when the tumor reaches 2 cm most of the patients have canal paresis. When the tumor is around 1 cm a large spread of canal paresis is seen, suggesting that many patients will start to have impaired vestibular function at this size. In study 4, we found an association between vHIT gain and tumor volume for lateral, anterior, and posterior canals and between canal paresis and tumor volume. No association between VEMPs and volume was found. Previous studies have found an association between larger tumors and one or more of canal paresis, lower vHIT gain or gain asymmetry, increased vHIT saccades and VEMP pathology,[94,95,97,111,122,133,135,139] while some of the associations were not found. Study 4 included smaller

tumors with a mean maximum tumor diameter of 10.5 mm and a relatively small spread of tumor size (2-22 mm).

12.3.2 Tumor size and dizziness

The largest tumors were not associated with more dizziness, and perhaps less, but this was only a trend. This paradox can be explained by several possible mechanisms.
Early detection: Patients who are dizzy will probably detect their VS early because their dizziness will lead to an MRI. They probably have their VS localized in a way that leads to dizziness.
Vestibular impairment occurs while a tumor is small: Ongoing vestibular impairment probably also leads to more vestibular symptoms, as described in section 12.3.1.
Central vestibular compensation; which is described in section 12.4.
In study 3, patients with a non-growing tumor showed no change in dizziness, objective unsteadiness and caloric function during long-term follow-up.
With a non-growing tumor, the patients will have time for central vestibular compensation. These findings are important in patient management and suggest that for a patient with a non-growing tumor, wait-and-scan can be recommended in terms of vestibular symptoms and function. As the increasing use of MRI will detect more small VS, there is reason to believe that in future there will be an increment of patients managed on a wait-and-scan basis.

12.3.3 Tumor growth and objective unsteadiness

In study 3 we found that unsteadiness on the platform for untreated VS patients predicted tumor growth within three years. This is a new finding, which is also confirmed by Higuchi et al.[140] Previously, two studies have found subjective unsteadiness to be associated with tumor growth[62 63] and in one study there was no such association.[8] We found no other predictors of tumor growth when including other potential predictors, such as initial tumor volume. The reason for this finding could be that central compensation is less effective in a tumor that grows. As tumor growth is the main factor determining treatment, these results suggest that patients

with objective unsteadiness have a higher risk of tumor growth and require close follow-up.

12.4 Central vestibular compensation

Central vestibular compensation may explain some of the apparent paradoxes found in this study. We found that 72% of patients had vestibular dysfunction, as indicated by a canal paresis on the caloric test at the time of diagnosis. However, the majority of patients reported mild vestibular symptoms, if any. There was a trend for fewer vestibular symptoms in the group with the largest tumors.

In study 2, there was no increase in vestibular symptoms or unsteadiness during long-term follow-up of patients with non-growing tumors. Among the general population, the prevalence of dizziness and unsteadiness increases with age.[141]

In both of these studies, the lack of vestibular symptoms in a large group of patients with a clear vestibular disorder is explained by central vestibular compensation.

In study 3, we found that objective unsteadiness predicted tumor growth. We have hypothesized that the rate of change, rather than absolute vestibular function, may determine unsteadiness. In other words, central compensation is less effective when tumor growth causes rapid loss of vestibular function.

The explanation for this discrepancy is that in VS, the loss of vestibular function occurs slowly, and that this allows sufficient time for effective central compensation.

12.5 Methodological considerations with strengths and limitations

To the best of our knowledge, study 1 was the first to analyze the association between subjective dizziness and objective findings related to tumor size, tumor location and vestibular function. Study 2 was the first longitudinal assessment of the combination of patient-reported dizziness, caloric function and objective postural instability. Study 3 was the first to report the predictive value of objective posturographic unsteadiness for tumor growth. Study 4 was the first to report comprehensive testing of vestibular

function on the tumor and non-tumor sides in relation to tumor volumetry in VS patients.

12.5.1 Patient selection

During this study, our hospital received the majority of patients in Norway with newly diagnosed VS. Since our hospital offers all treatment modalities, including gammaknife radiosurgery, microsurgery and wait-and-scan, the risk of selection bias is minimal. Nevertheless, we selected subgroups of VS patients for our various different studies.
Study 1 included all tumor sizes and treatment modalities. Study 2 focused on patients with small- to medium-sized tumors that did not grow during follow-up. Study 3 focused on patients initially selected for wait-and-scan management. In study 4, only patients with small to medium-sized tumors initially selected for wait-and-scan management were included. The selection of subgroups of patients in some of the studies entails that the results may not necessarily be generalized to all VS patients. For example, in study 4, the inclusion of patients with larger tumors would probably result in a higher prevalence of abnormal findings. However, great majority of patients referred to our hospital today present with small- to medium-sized tumors.

In the longitudinal studies, very few patients were lost to follow-up and consequently the risk of attrition bias was low.

12.5.2 Missing data

We have considered the potential impact of missing data on the results of this thesis. Particular attention was given to missing data for tumor measurements, caloric function, posturographic unsteadiness, and patient-reported symptoms.

Tumor measurements were available for almost all patients at baseline, as well as follow-up, and the risk of bias due to missing data was considered to be very low.

Patient-reported symptoms collected in questionnaires were also available for most patients at baseline. In study 1, we showed that patients without questionnaires were similar to the others with respect to symptoms reported by the treating physician, leading to low risk of bias.

Caloric testing was not performed routinely for all patients before June 2003, and consequently data on caloric function was missing for some patients in studies 1-3. We have assessed whether before June 2003 caloric testing was performed for particular medical indications. However, we found this not to be the case, and that missing data in this time period was due to random logistical factors, and that the risk of bias due to missing data was low.

Posturography data was missing for less than 10% of the patients in studies 1-3, and the risk of bias was considered to be low.

12.5.3 Vestibular symptom reporting and postural unsteadiness

In this study, we used a VAS scale to measure dizziness. The visual analog scale is a versatile instrument for quantifying subjective symptoms with high precision on a continuous scale from zero to hundred. It is a simple method in which the patients rate their own symptoms. Patients were asked to respond to the question: "How troublesome is your dizziness usually?" For this reason, we assumed a good validity of the VAS scores for dizziness severity. However, other instruments have been more extensively validated for dizzy patients, including the Dizziness Handicap Inventory (DHI) and Vertigo Symptom Scale. The VAS scores in our study showed a distribution that was very similar to the DHI scores from previous studies of VS patients.[3,142]

A strength of this study is that postural balance was measured objectively by platform posturography. Posturography ensures valid measures of postural balance with high precision that can be compared with normative data. It is also highly sensitive to changes over time in a patient cohort. In this study, two different methods of

posturography were used. However, each patient was evaluated using the same method during the entire follow-up, and for study 2 we performed an analysis for the two methods separately, with no change in the conclusion.
Moreover, both methods are designed to measure the same property, postural instability, although in slightly different ways.
The dynamic platform may possibly be more sensitive to peripheral vestibular dysfunction than the static platform. Ideally, future studies should use the dynamic platform to measure postural instability in VS patients.

12.5.4 Vestibular tests

In this study, we have included the most relevant modern tests of vestibular function. These tests measure the five vestibular end-organs, and thereby both divisions of the vestibular nerve. The same tests were performed for a large group of untreated VS patients and the results were related to tumor volume. We also report abnormal results on the non-tumor side, which is an outcome that was often omitted in previous studies. We used predefined criteria for abnormal catch-up saccades and four of the authors formed a focus group that reviewed all the vHIT results for pathology.

The first three studies did not include vHIT or VEMPs, so that some patients with vestibular pathology may have been missed. In the first study, these tests might have resulted in a greater correlation between vestibular symptoms and nerve function. However, this would not have changed the general conclusions of the article. Further studies are necessary to determine whether or not vHIT and VEMP change during long-term follow-up of non-growing tumors, or whether these tests may predict tumor growth.
The vHIT and VEMP methods are subject to development. The techniques, as well as the interpretation of the results, are being refined.

VS patients often have a compensated or good vestibular function. The results from our study therefore cannot necessarily be generalized to other acute or episodic vestibular diseases such as vestibular neuritis and Menière's disease. We examined

small to medium-sized schwannomas (< 25 mm) and the results are not necessarily representative for larger tumors.

For the relatively new vHIT and VEMPs vestibular function tests, there is no consensus regarding the methods or the definition of a pathologic result.
Different criteria are used to define vHIT as pathologic: pathologic gain and/or pathologic saccades. The definition of a pathologic saccade may also vary.
In some patients, there might be difficulties concerning how to separate an abnormal result from an artefact or a normal result.[108] The fact that a decreased vestibular function on one side can also generate a pathologic vHIT result in the healthy ear[74] may complicate the interpretation of the results. A subjective evaluation of both sides together will probably reduce the prevalence of abnormal test results on the non-tumor side, due to more pathology in one side relative to the other. The subjective evaluation seems to be more important for vHIT than for VEMP, and less important for caloric test.
VEMP is often defined as pathologic, based on an abnormal asymmetry ratio, but the cut off varies. Some studies describe whether there is a VEMP response or not, and often only the results on the tumor side are reported. This will result in an altered sensitivity, because they will miss the one with a lower response on one side relative to the other side, and likewise gain an uncertain high sensitivity for patients that have no response on either side.
Collecting our own normal material for testing could reduce uncertainty to some extent. We relied on others' cut-off values for VEMPs, obtained from a study that had collected their own normal material.[111] For vHIT, we used the cut-off values integrated in the software.[143] However, there would still be other sources of uncertainty that may affect test results, such as the definition of a pathologic saccade.

12.5.5 Tumor volume as a measure of tumor size

The use of volumetric tumor measurement in studies 3 and 4 is a strength, as tumor volume has been shown to be the most sensitive method for detecting changes in VS size.[56-58] The examiner that performed the measurement was also blinded for clinical

information. In retrospect, we would have preferred the more reliable tumor volume as a measure of tumor size in study 1.

13. CONCLUSIONS

In this thesis we found that one third of patients with untreated vestibular schwannoma did not report any dizziness, which was reassuring for the patients. Particularly for the 9% of patients that did report severe dizziness, it was important to also consider the impact of other vestibular diseases and to consider vestibular rehabilitation. Around one third of the patients had moderate to severe dizziness and the prevalence was associated with canal paresis and postural instability. Surprisingly, we found no relationship between dizziness and tumor size.

Furthermore, the prevalence of moderate to severe dizziness, postural instability and canal paresis were unchanged during long-term follow-up of untreated VS patients without growth of tumor, indicating a good prognosis regarding vestibular symptoms and function in the wait-and-scan group.

We found that unsteadiness measured by posturography predicts growth of untreated VS within three years. The reason for this may be progressive vestibulopathy, with less time for central compensation. These results suggest that patients with postural instability have a greater risk of tumor growth and require closer follow-up. The results needs to be confirmed by other studies.

We compared the new vHIT, cVEMP and oVEMP vestibular tests with the caloric test, and found that the caloric test and vHIT were the most sensitive tests, with sensitivities of 47% and 51%, respectively. The sensitivity of the caloric test and vHIT were found to be volume-dependent. One limitation of vHIT was the high prevalence of abnormal results, also in the non-tumor side, and that performing lateral canal vHIT did not provide additional information when a caloric test was normal. The combination of caloric test and cVEMP increased the sensitivity to 65% and showed a low prevalence of abnormal results in the non-tumor side, and therefore a reasonable choice in detecting vestibulopathy in the superior and inferior nerves.

Performing all tests increased the sensitivity, but also the prevalence, of abnormal results on the non-tumor side, making the clinical relevance more questionable.

14. FUTURE PROSPECTS

In this thesis, the VS' impact on vestibular symptoms and function were investigated. The results show a good long-term prognosis for untreated VS patients. When informing a patient with a chronic disease of the different treatment options, it is important for the patient to have knowledge about the natural course of the disease. We now include our findings from this study when informing VS patients.

Study 1 showed that only a few patients suffer severe dizziness. Future studies should examine this specific subgroup in terms of how symptoms and comorbidities differ from the larger group. Additionally, further research should focus on identifying the most effective treatment options for this subgroup, such as the role of gentamycin treatment.

The long-term observation of untreated VS patients who did not experience tumor growth revealed no deterioration in vestibular symptoms and function. These findings are reassuring, yet future studies should examine whether vestibular rehabilitation of symptomatic patients leads to a reduction of dizziness and unsteadiness during long-term follow-up. Furthermore, future studies of vestibular symptoms should incorporate validated schemes, such as the VSS.

Our results showing increased unsteadiness on posturography for patients with tumor growth suggest that unsteady VS patients may require closer monitoring for tumor growth and perhaps more active treatment. This finding should be confirmed by other studies.

In our last study, we compared the newer vHIT, cVEMP and oVEMP vestibular tests and the traditionally used caloric test for VS patients with small- to medium-sized vestibular schwannoma. The results indicate that the caloric test is still one of the most sensitive tests for detecting vestibulopathy in VS patients and will continue to be used at our department. Future studies should also study these tests' sensitivities

for larger VS tumors and for other vestibular diseases such as Menières disease, bilateral vestibulopathy, and vestibular neuritis. Furthermore, the institution should preferably have their own normal material for these tests.

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16. Publications

I

Predictors of vertigo in patients with untreated vestibular schwannoma

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Short running head: Vertigo in vestibular schwannoma patients

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Abstract

Objectives: Previous studies have shown that vertigo is the most powerful negative predictor of quality of life in patients with vestibular schwannomas, but the variability in vertigo symptom severity is still poorly understood. We wanted to find out whether vertigo could be related to objective parameters such as tumor size, location, vestibular nerve function, hearing and postural stability in patients with untreated vestibular schwannomas.

Study design: Baseline data from prospective cohort study.

Setting: Tertiary referral center.

Patients: 434 consecutive patients with unilateral VS diagnosed on MRI. Mean age 56 years (range 16–84 years). 53 % women.

Intervention: Diagnostic, with a medical history, otolaryngological examination, pure tone and speech audiometry, MRI, posturography, and videonystagmography with bithermal caloric tests.

Main outcome measure: Dizziness measured on a 100 mm visual analog scale (VAS). Secondary outcome measures were canal paresis and postural imbalance (static and dynamic posturography).

Results: 303 patients (70 %) completed the VAS. Severe dizziness, defined as VAS ≥ 75, was reported by 9 % of the patients. Larger tumors were associated with higher risk of postural instability and canal paresis. Moderate to severe dizziness was associated with postural imbalance and canal paresis, and possibly with small to medium sized tumors.

Postural instability was related to tumor size and canal paresis when measured by dynamic, but not with static, posturography.

Conclusion: A minority of VS patients experience severe vestibular symptoms related to canal paresis and postural instability. A curvilinear relationship is hypothesized between tumor size and dizziness.

Introduction

Vestibular schwannoma (VS) is one of the most well-defined peripheral vestibular disorders, but the remarkable variability in vertigo symptom severity[1] is not completely understood. Most patients present with unilateral hearing loss (94 %) and tinnitus (83 %)[2]. Vestibular symptoms such as vertigo, nausea, lateropulsion and nystagmus are often mild, due to slow tumor growth and central compensation, but nevertheless present in 40–75 % of the patients at the time of diagnosis[1–7]. A minority of patients report severe vertigo. In a previous study, we showed that, when present, vertigo is the most debilitating symptom with respect to health related quality of life[8]. Lloyd et al confirmed this finding[9]. In a recent study, we found that vertigo in VS patients also represents a risk factor for future work disability[10].

VS management has traditionally focused on tumor growth, facial nerve function and hearing outcomes, while outcomes related to vertigo and dizziness are rarely reported. Given the high impact of vestibular symptoms on patients' quality of life and work disability, there is a need to examine these symptoms more carefully.

The primary aim of this study was to find out whether vertigo symptom severity in patients with untreated VS was associated with known objective factors such as tumor size, location, vestibular nerve function and postural imbalance.

Materials and methods

The study included 434 consecutive patients with newly diagnosed, untreated, unilateral vestibular schwannoma on MRI. The inclusion period was from 2001 to 2010. The mean age was 56 years (range 16–84 years), 53 % were women. Men were somewhat younger than women (mean 54 vs 58 years, t-test: $p = 0.002$).

The examination included a medical history, otolaryngological examination, pure tone and speech audiometry, posturography, and videonystagmography with bithermal caloric tests. Symptoms were evaluated through questionnaires.

MRI evaluation

Complete MRI-data were available for 429 patients. The median tumor size was 13 mm (interquartile range 12 mm, range 2–55 mm). 26 % were intrameatal. Older patients tended to have smaller tumors (linear regression: $p < 0.0005$). The tumors were measured in three planes on MRI (T1 contrast axial and coronal MRI). Tumor location was classified as extrameatal or intrameatal depending on whether or not the tumor extended into the cerebellopontine angle. Tumor size was defined as the largest diameter. In predominantly extrameatal tumors the intracanalicular component was not included in this measure. Intrameatal tumors were smaller than extrameatal ones (Mann-Whitney U: $p < 0.0005$).

Audiometry

Hearing was measured using bilateral pure-tone air-conducted audiometry and monosyllable speech discrimination (SD). The pure-tone average (PTA) was the arithmetic mean of the frequencies 0.5, 1, 2 and 3 kHz.

Measurement of postural imbalance

Static posturography was performed using a force platform (Cosmogamma®, Bologna, Italy) containing three pressure transducers. The movement of the center of pressure was measured while the patient was standing quietly for one minute with eyes open and eyes closed. The path length with eyes closed was used for statistical analysis. This method was used for 226 of the patients.

Since 2006, postural imbalance was measured using *Dynamic Posturography* (EquiTest®, NeuroCom®, USA) and the Sensory Organization Test (SOT) protocol. This method was used for 153 of the patients and involved measuring postural sway under six different sensory conditions. Condition 1 (SOT1): visual surround stable, eyes open, platform stable. Condition 2 (SOT2): visual surround stable, eyes closed, platform stable. Condition 3 (SOT3): visual surround moves, eyes open, platform stable. Condition 4 (SOT4): visual surround stable, eyes open, platform moves. Condition 5 (SOT5): visual surround stable, eyes closed, platform moves. Condition 6 (SOT6): visual surround moves, eyes open, platform moves. The composite score was calculated by independently averaging the equilibrium scores for conditions 1 and 2, adding these two scores to the equilibrium scores from each trial of sensory conditions 3, 4, 5 and 6, and dividing the sum by 14. Missing trials in conditions 3, 4, 5 and 6 were replaced by the average

93 equilibrium score for that condition.
94
95 For static posturography postural sway was defined as the path length in mm with eyes
96 closed. For dynamic posturography the composite score was used.
97
98 *Caloric testing*
99 Bithermal caloric tests were performed with cold and hot water at 30 and 44 degrees
100 centigrade respectively. Each of the four irrigations lasted for 30 s. Slow phase
101 nystagmus velocities were recorded by videonystagmography (Hortmann, Germany).
102 Canal paresis was defined as unilateral weakness greater than 25 % calculated using
103 Jonkees´ formula[11]. Caloric testing was included into the testing protocol from June 2003
104 and completed in 239 patients.
105
106 *Vertigo symptoms*
107 All patients filled in a questionnaire where they were asked to quantify their dizziness on
108 a 100 mm visual analog scale (VAS) ("How troublesome is your dizziness usually?"). In
109 order to make interpretation of the VAS scores more intuitive, we used a grading system
110 and cut points developed for pain[12]. A VAS score 0 to 4 mm was classified as "no
111 dizziness", a score of 5 to 44 mm was classified as "mild dizziness", a score of 45 to
112 74 mm was classified as "moderate dizziness", and a score of 75 to 100 mm was
113 classified as "severe dizziness". The patients were also asked to characterize their
114 dizziness during the last three months ("spinning", "rocking", "walking on air", "attacks",
115 "other"). The VAS questionnaire was completed by 303 patients (70 %). The responders

were similar to the non-responders with respect to dizziness reported by the interviewing physician, who filled in a questionnaire after each interview including a question whether or not the patients had complaints of dizziness (48 % vs 41 %, chi-square: $p = 0.2$), thus minimizing the risk of non-responder bias.

Statistical Analysis

Statistical analysis was performed with STATA software (StataCorp, USA) using logistic regression. The dependent variables were moderate to severe dizziness defined as VAS > 44 mm, canal paresis > 25 % and unsteadiness defined as performance in the lower quartile on either of the two posturography platforms. The independent variables were age, sex, tumor size, intrameatal tumor location, hearing level (PTA on tumor side) and speech discrimination on the tumor side. A univariate analysis (unadjusted) is reported together together with a multivariate with stepwise backward-selection estimation based on a significance level of $p \geq 0.2$ as removal criterion from the model.

All variables were examined for extreme values, visually assessed by histograms and scatterplots and tested for normal distribution by Shapiro-Wilk test. No outliers were removed. Non-parametric tests were used when indicated as specified in the results. P-values less than 0.05 were considered significant.

Results

Dizziness

VAS scores for dizziness are shown in figure 1. Based on these scores 35 percent of the patients reported no dizziness, while mild, moderate, and severe dizziness was reported by 34, 22, and 9 percent respectively. Spinning vertigo was reported by 24 % of patients with moderate to severe dizziness and by 11 % of patients with mild dizziness (chi-square: $p = 0.003$). Moderate to severe dizziness was associated with postural imbalance and canal paresis (table 1). The association between dizziness and postural imbalance was confirmed also on analysis (linear regression and Spearman correlation: $p < 0.01$) of each of the posturography methods separately. A possible association was found between moderate to severe dizziness, poor hearing and smaller tumors. In the multivariate model, the four variables postural imbalance, canalparesis, tumor size and intrameatal tumor location taken together explained approximately 10 % of the variance in dizziness severity ($p = 0.0001$). Figure 2 shows the relationship between tumor size and dizziness severity indicating a trend for less dizziness in tumors > 20 mm (Mann-Whitney-U: $p = 0.07$).

Canal paresis and pure tone hearing

Out of 239 patients 72 % had significant (> 25 %) canal paresis. With tumors larger than 20 mm the proportion with canal paresis rose to to 93 % (Figure 3). Logistic regression analysis of factors associated with canal paresis is shown in table 2. Canal paresis was associated with larger tumors. Figure 3 shows the relationship between tumor size, canal paresis and pure tone hearing. Differences in tumor size explained 18 % of the variance in canal paresis and 1 % of the variance in hearing (pure tone average). The association between canal paresis (absolute value of unilateral weakness) and pure tone average was

statistically significant (linear regression: $p = 0.03$), but weak ($R^2 = 0.02$). A possible association (trend) was found between canal paresis and poor hearing.

Postural imbalance

Logistic regression analysis of factors associated with postural imbalance—defined as performance in the lower quartile while standing with eyes closed—is shown in table 3. The results on the static and dynamic platforms differed with respect to associations with the dependent variables. Whereas on the static platform a possible association was found between postural sway, higher age and poor hearing, on the dynamic platform, sway was associated with tumor size. Linear regression (univariate) showed that of the six subtests in the SOT condition 5 was the one that correlated best with tumor size ($R^2 = 0.08$, $p = 0.01$). This subtest also correlated with canal paresis ($R^2 = 0.08$, $p = 0.001$).

Discussion

In spite of their slow growth, vestibular schwannomas may cause acute vestibular failure, characterized by the combination of vertigo (usually a false sense of spinning) with nausea, vomiting, lateropulsion to the lesioned side, and nystagmus to the contralesional side. In this study a minority of the patients (11 %) reported spinning vertigo. However, in most cases the vestibular loss occurs gradually, and due to central compensation, symptoms may be minimal or absent, as testified by the fact that 35 % of the patients in our study reported no dizziness. In this study we did not distinguish strictly between vertigo and dizziness. However, patients with moderate to severe dizziness were more likely to characterize their problem as a sensation of spinning.

Vertigo and dizziness are subjective sensations that may be caused by a variety of disorders. These symptoms are sometimes, but not always, related to objective postural instability. Vertigo is thought to arise from a sensory mismatch in the cortex of the brain between perceived and expected visual and vestibular stimuli, while objective postural instability may arise from a large number of neurological and orthopedic disorders. Even in patients with a well-defined vestibular disorder, such as vestibular schwannoma, vertigo and postural imbalance are clearly different phenomena since less than 10 % of the variance in subjective dizziness (VAS) could be explained by differences in objective postural stability (SOT). In other words, dizziness could not be predicted reliably based on objective postural sway.

Postural sway can be measured in different ways, and how it is measured seems to affect how well it correlates with disease-related parameters such as tumor size, canal paresis etc. In this study, static posturography, i.e. postural sway when standing on a firm, stable surface with eyes closed, did not correlate with tumor size or canal paresis. It seemed to correlate with age, and there was possibly a gender difference. The other method used in this study—dynamic posturography—seemed to be more relevant, since particularly the fifth condition (SOT5), i.e. postural sway with eyes closed on a moving (sway-referenced) platform, correlated with both tumor size and canal paresis. This method is therefore more useful when measuring postural instability in patients with vestibular schwannomas.

Tumor size and growth rate have important clinical implications for therapy and prognosis. In this study only tumor size was evaluated. Larger tumors were associated with increased risk of canal paresis and increased postural instability. It is hardly surprising that tumor growth causes loss of nerve function in untreated schwannomas. However, it may be surprising that tumor size matters so little. Differences in tumor size can only explain about 18 % of the variance in canal paresis and 1 % of the variance in pure tone hearing level (PTA). Other factors must therefore be of importance. It may also seem contradictory that dizziness appeared to be associated with smaller tumors in the multivariate analysis. However, in theory, the relationship between tumor size and dizziness could be curvilinear. If so, the smallest tumors would tend to be asymptomatic due to normal nerve function. Medium-sized tumors would tend to cause increasing neuropathy associated with dizziness and vertigo. Larger tumors would be associated with a more complete and more stable peripheral loss, allowing for better central compensation. Further growth could cause increasing symptoms due to compression of the brainstem and cerebellum, however, in our material such large tumors were few. Our data provides some support for this hypothetical curvilinear relationship between tumor size and dizziness (figure 2).

Tumor location could be of importance to nerve function. In our study, intrameatal tumor location was associated with lower risk of canal paresis, but after adjustment for tumor size, the effect disappeared. Intrameatal tumors are smaller and may have less growth potential than extrameatal ones. We therefore cannot conclude that the tumor location within the internal auditory canal in itself is of importance for vestibular nerve function.

It would be of interest to know whether the nerve passes through the tumor or mostly lateral to it, however this information is not available preoperatively.

The vestibular and cochlear nerves appear to live separate lives in patients with vestibular schwannomas in spite of their close proximity. Although vestibular function, as measured by the caloric response, was associated with pure-tone hearing level, the relationship was very loose. Only 2 % of the variance in caloric response could be explained by differences in hearing level.

In theory, assessment of vestibular nerve function should be the key to understanding dizziness in patients with vestibular schwannomas. However, this is only partly true because central vestibular compensation usually gives effective symptom relief even after complete section of one vestibular nerve. It is even more effective when vestibular function is lost gradually due to a slow-growing tumor such as a vestibular schwannoma. Vestibular nerve function can be measured in many different ways. We used the caloric test because this was the only method available to us at the time of the study. Canal paresis correlated with tumor size, symptom severity and postural sway (SOT5). Still the proportion of the variance in dizziness severity that could be explained by canal paresis, postural instability, tumor size and location was only 10 %. This is not surprising, since studies of outcomes after other vestibular disorders, particularly vestibular neuritis[13], show little correlation between symptoms and caloric function. There are several other and more novel ways of measuring the function of the vestibular nerve, including head impulse testing and measurements of cervical and ocular myogenic potentials in response

to sound or vibrations. The caloric test measures the function of the superior branch of the vestibular nerve. A more comprehensive examination of vestibular function might lead to better understanding of the causes of dizziness. However, reported vestibular symptoms are probably multifactorial, depending on nerve function, central compensation as well as comorbid and psychological factors.

It has been speculated that a complete vestibular deafferentation is better than a partial loss, because it removes disturbing peripheral signals that may prevent efficient central compensation. This is certainly the case in patients with vertigo attacks due to Menière's disease, who often experience a significant improvement after medical or surgical destruction of the labyrinth or after vestibular nerve section. Our study offers some arguments to this effect in vestibular schwannomas. Larger tumors were associated with more canal paresis, but not with more—possibly even less—dizziness. Some reports indicate that surgery may improve symptoms in vestibular schwannomas patients suffering from severe vertigo[14]. However, symptoms also improve with observation[15]. In our clinic, vestibular schwannoma patients who experience severe vertigo undergo broad neurotological investigation looking for other comorbid factors. Conservative measures, including counseling and vestibular rehabilitation, are the first line of treatment unless surgery is indicated for other reasons.

Finally, a remark is due on the possible strengths and limitations of the present study. Its strengths are mainly in its size and prospective design, as well as in the analysis of the correlation between subjective dizziness and objective findings related to tumor size and

vestibular nerve function, which to the authors' knowledge has not been published before. Its limitations are mainly in the fact that not all of the patients received all of the tests, which reduces the number of observations in some of the analyses (as specified in the tables). Moreover, the VAS scale is not a validated tool for the assessment of dizziness. It has been used extensively in the quantification of pain[12], and in this study, VAS-scores showed a distribution very similar to that from a previous study of VS-patients using the Dizziness Handicap Inventory[1].

Conclusion

Subjective dizziness and vertigo in vestibular schwannoma patients is associated with canal paresis and postural instability. The latter two factors are in turn associated with larger tumors. Dynamic posturography seems to correlate better than static posturography with tumor size and canal paresis. This study found no simple linear relationship between tumor size and dizziness. A possible curvilinear relationship is hypothesized based on the interaction between loss of nerve function and central compensation.

Conflict of interest: None declared.

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Figure legends

Figure 1: Dizziness severity in 303 patients with untreated vestibular schwannomas. Patient responses to the question “How troublesome is your dizziness usually?” on a 100 mm visual analog scale.

Figure 2: Dizziness severity in four tumor size groups (largest diameter). Patient response to the question “How troublesome is your dizziness usually?” on a 100 mm visual analog scale. Box plot showing range (whiskers), quartiles (box) and median (black line).

Figure 3: Scatterplot showing the relationship between tumor size and canal paresis on the left panel and hearing loss on the right panel. Tumor size was defined as the largest tumor diameter in mm on MRI. Hearing loss is defined as pure tone average (0.5, 1, 2 and 3 kHz) in dB_{HL}. Linear regression analysis showed significant relationships at $p < 0.05$, but only 18 % of the variance in canal paresis and 1 % of the variance in hearing loss could be explained by differences in tumor size.

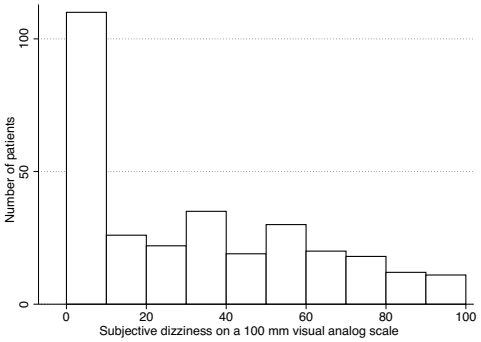


Figure 1

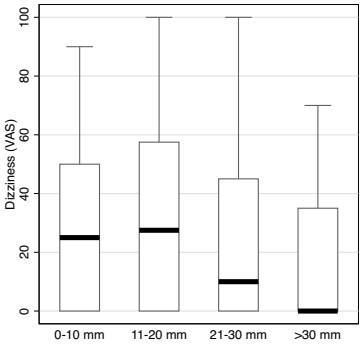
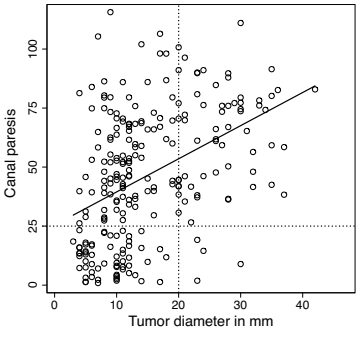


Figure 2



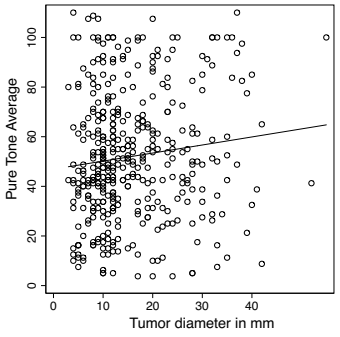


Figure 3

Table 1. Logistic regression analysis of factors associated with moderate to severe dizziness (VAS > 44 mm*) in 303 patients with untreated vestibular schwannoma

Variable	Observations	OR	P-value
Univariate (unadjusted OR)			
Age (years)	303	1.01	0.2
Female sex	303	1.40	0.2
Tumor size (mm)	299	0.99	0.4
Intrameatal tumor location	302	0.89	0.7
Hearing level (PTA in dB_{HL})	291	1.01	0.04
Speech discrimination (%)	291	0.99	0.006
Canal paresis > 25 %	210	2.81	0.01
Postural imbalance†	279	2.67	0.001
Multivariate (adjusted OR)			
Postural imbalance†	193	3.94	0.001
Canal paresis > 25 %	193	3.43	0.006
Tumor size (mm)	193	0.94	0.02
Intrameatal tumor location	193	0.50	0.1

*Score on a 100 mm visual analogue scale responding to the question "How troublesome is your dizziness usually?".

†Postural imbalance was defined as performance in the lower quartile on either of the two posturography tests (SOT or CSS).

Table 2. Logistic regression analysis of factors associated with canal paresis > 25 % in 239 patients with untreated vestibular schwannoma

Variable	Observations	OR	P-value
Univariate (unadjusted OR)			
Age (years)	239	0.99	0.6
Female sex	239	0.78	0.4
Tumor size (mm)	237	1.17	< 0.0005
Intrameatal tumor location	239	0.30	< 0.0005
Hearing level (PTA in dB_{HL})	235	1.01	0.03
Speech discrimination (%)	229	0.99	0.01
Multivariate (adjusted OR)			
PTA (dB_{HL})	226	1.01	0.1
Tumor size (mm)	226	1.16	< 0.0005

Table 3. Logistic regression analysis of factors associated with postural instability* in 239 patients with untreated vestibular schwannoma

	Computerized Static Stabilometry		
Variable	Observations	OR	P-value
Univariate (unadjusted OR)			
Age (years)	226	1.04	0.007
Female sex	226	0.84	0.6
Tumor size (mm)	223	1.00	0.9
Intrameatal tumor location	225	0.69	0.3
Hearing level (PTA in dB_{HL})	218	1.02	<0.0005
Speech discrimination (%)	224	0.99	0.02
Canal paresis > 25 %	100	1.98	0.2
Multivariate (adjusted OR)			
Age (years)	98	1.04	0.08
Female sex	98	0.35	0.05
Hearing level (PTA in dB_{HL})	98	1.03	0.02
	Sensory Organization Test		
Variable	Observations	OR	P-value
Univariate (unadjusted OR)			
Age (years)	153	1.02	0.3
Female sex	153	1.79	0.1
Tumor size (mm)	152	1.05	0.02
Intrameatal tumor location	153	0.86	0.7
Hearing level (PTA in dB_{HL})	148	1.01	0.08
Speech discrimination (%)	142	0.99	0.003
Canal paresis > 25 %	130	2.59	0.1
Multivariate (adjusted OR)			
Speech discrimination (%)	119	0.98	0.01
Tumor size (mm)	119	1.08	0.04
Intrameatal tumor location	119	3.73	0.06
Age (years)	119	1.03	0.2

*Postural imbalance was defined as performance in the lower quartile on either of the two posturography tests (SOT or CSS).

II

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Long-term Effects of Conservative Management of Vestibular Schwannoma on Dizziness, Balance, and Caloric Function

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Abstract

Objectives. To study the development of dizziness, caloric function, and postural sway during long-term observation of untreated vestibular schwannoma patients.

Study Design. Retrospective review of a prospectively maintained longitudinal cohort.

Setting. Tertiary referral hospital.

Subjects and Methods. Patients with vestibular schwannoma undergoing wait-and-scan management were included—specifically, those who did not require treatment during a minimum radiologic follow-up of 1 year. Baseline data and follow-up included magnetic resonance imaging, posturography, bithermal caloric tests, and a dizziness questionnaire. Main outcomes were prevalence of moderate to severe dizziness, canal paresis, and postural instability at baseline and follow-up, as compared with McNemar's test.

Results. Out of 433 consecutive patients with vestibular schwannoma, 114 did not require treatment during follow-up and were included. Median radiologic follow-up was 10.2 years (interquartile range, 4.5 years). Age ranged from 31 to 78 years (mean, 59 years; SD, 10 years; 62% women). Median tumor volume at baseline was 139 mm^3 (interquartile range, 314 mm^3). This did not change during follow-up ($P = .446$). Moderate to severe dizziness was present in 27% at baseline and 19% at follow-up ($P = .077$). Postural unsteadiness was present in 17% at baseline and 21% at follow-up ($P = .424$). Canal paresis was present in 51% at baseline and 56% at follow-up ($P = .664$).

Conclusions. There was no significant change in the prevalence of dizziness, postural sway, or canal paresis during conservative management of vestibular schwannoma, while tumor volume remained unchanged. This indicates a favorable prognosis in these patients with regard to vestibular symptoms.

Keywords

vestibular schwannoma, acoustic neuroma, long-term prognosis, posturography, balance, vertigo, dizziness, caloric test, untreated, conservative management, observation

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Conservative management of vestibular schwannomas with regular magnetic resonance imaging (MRI) has become a common strategy in recent years. With the increased availability of MRI, this ''wait and scan'' policy has become feasible due to the fact that about 50% of small- to medium-sized tumors do not grow when observed for 5 years.[1] Other management options are mainly gamma knife radiosurgery (GKR) or microsurgical removal of the tumor. Since vestibular schwannoma is rarely fatal today, the choice among these management modalities is increasingly aimed at preserving the quality of life of the patient.

The most common symptoms in patients with untreated vestibular schwannoma are unilateral hearing loss (94%-97%), tinnitus (73%-83%), unsteadiness (33.5%-63%), and vertigo (20%-49%).[2-9] We were the first to demonstrate that

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vertigo is the strongest negative predictor of quality of life in patients with vestibular schwannomas. Quality of life is also affected by unsteadiness.[10] These observations were confirmed by others.[3,11-13]

Andersen et al[14] found that 9% of patients with newly diagnosed vestibular schwannoma reported severe dizziness. We do not fully understand why some patients become dizzy while others do not, but tumor growth, fluctuations in vestibular function, and comorbidities are likely explanations for the vestibular symptoms in a majority of cases.

Usually, vestibular compensation will lead to relief from severe dizziness in most patients,[15] despite damage to the vestibular nerve. Tumor growth is believed to disturb the vestibular compensation.

Given the impact of vestibular symptoms on quality of life, it is necessary to know the progression of vestibular function and symptoms if the tumor is left untreated. With regard to subjective vestibular symptoms, there are limited long-term data.[12,16-18] No previous study has, to our knowledge, reported the long-term development of postural control during conservative management.

The aim of this study was to investigate the long-term consequences of conservative vestibular schwannoma management on dizziness, postural instability, and caloric function.

Materials and Methods

Patients, Design, Treatment Algorithm, and Ethics

This is a retrospective study of a subset of 433 patients newly diagnosed with sporadic unilateral vestibular schwannoma who were included into a prospectively maintained database. The 433 patients were included between September 2001 and March 2010 and followed up at regular intervals (6 months and 1, 2, 5, and 10 years). Data on management, tumor size, clinical symptoms, hearing, and vestibular function were recorded.[10] Our management algorithm and methods for estimating tumor volumes from MRI scans were published earlier.[19]

The patients were elected for conservative management, GKR, or microsurgery according to the following algorithm based on tumor size and growth: conservative management (wait and scan) if the tumor was <20 mm; GKR for tumors of 20 to 25 mm or smaller, if there was documented growth on serial MRI; and microsurgery for tumors >25 mm.

For the present study, we identified and included patients who, by August 2018, still underwent conservative management and had both MRI and either caloric tests or clinical data at 2 time points over an interval of at least 1 year.

The database and its use for scientific studies were approved by the Norwegian National Data Inspectorate (NSD 13199), and all patients gave their written informed consent at inclusion.

Data Collection for the Present Study

For the present study, we used data on MRI, posturography, and bithermal caloric tests. A questionnaire was filled in, including visual analog scale (VAS) scores for vertigo symptoms, time course, and characteristics of dizziness.

Static posturography was carried out with a force platform (Cosmogamma, Bologna, Italy) containing 3 pressure transducers. The movement of the center of pressure was measured while the patients were instructed to stand still and maintain their balance for 1 minute—both with eyes open and with eyes shut. For statistical analysis, the path length in millimeters with eyes closed was used. For patients undergoing static posturography at baseline, this method was also used at follow-up.

Since 2006, postural balance for new patients was measured with dynamic posturography (EquiTest; NeuroCom, Pleasanton, California) and the sensory organization test protocol. This method involved measuring postural sway under 6 sensory conditions where a combination of movement of platform and the visual surroundings was used to challenge the vestibular component of the balance. The composite score was calculated and used for measuring postural sway. These procedures were described in a previous study.[14]

For static posturography, postural sway was defined as the path length in millimeters with the eyes closed. The composite score was used for dynamic posturography.

Caloric Testing

Slow-phase nystagmus velocities were measured by videonystagmography (GN Otometrics, Pleasanton, California) after 30 seconds of irrigation with cold (30°C) and hot (44°C) water into the external auditory canal. Canal paresis was defined as unilateral weakness >25% calculated with Jongkees's formula.[20]

Dizziness Symptoms

To quantify dizziness, the patients were asked to answer the question "How troublesome is your dizziness usually?" on a 100-mm VAS. To make interpretation of the VAS scores more intuitive, we used a grading system and cut points developed for pain[21]: a VAS score ranging from 0 to 4 mm, "no dizziness"; 5 to 44 mm, "mild dizziness"; 45 to 74 mm, "moderate dizziness"; and 75 to 100 mm, "severe dizziness."

The patients were also asked about the time course of their dizziness (attacks, periods, constant or no dizziness) and characteristics of dizziness (spinning, rocking, walking on pillows, and other) during the last 3 months.

Statistical Analysis

Stata/SE 15.1 software (StataCorp, College Station, Texas) was used for statistical analysis. The dependent variables were moderate to severe dizziness defined as VAS >44, canal paresis >25%, and unsteadiness on either of the 2 posturography platforms. Normative values between age groups given by NeuroCom International[22] were used to define cut points for unsteadiness on the dynamic platform. In static posturography, unsteadiness was defined as path length >1600 mm when performed with the eyes closed.[23]

Table 1. Change in Number of Patients with Dizziness, Unsteadiness, and Canal Paresis from Baseline to Follow-up.

	Follow-up			Follow-up			Follow-up	
Dizziness[a] (n = 100)	Yes	No	Unsteadiness (n = 104)	Yes	No	Canal Paresis (n = 72)	Yes	No
Baseline			Baseline			Baseline		
Yes	15	12	Yes	13	5	Yes	28	9
No	4	69	No	9	77	No	12	23

[a]Moderate to severe dizziness.

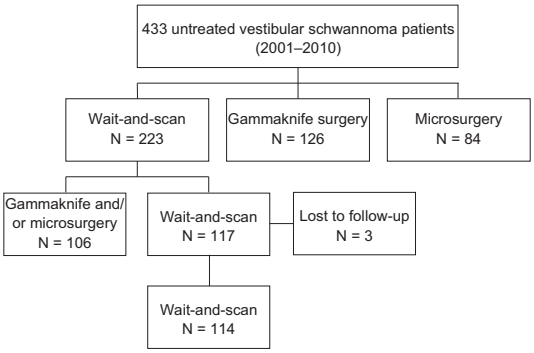

Figure 1. Flow diagram showing treatment of 433 patients with vestibular schwannoma, resulting in the inclusion of 114 participants in the present study by August 2018.

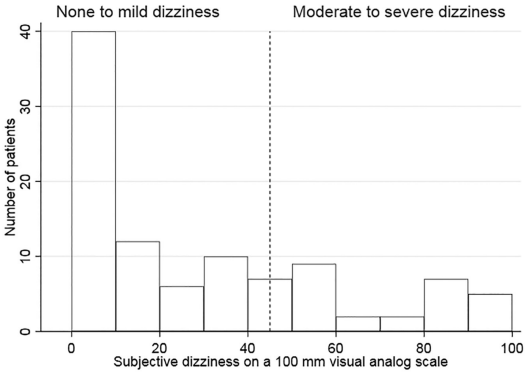

Figure 3. Distribution of visual analog scale score at baseline in 100 patients with untreated vestibular schwannomas. Dotted line indicates cut point between mild and moderate dizziness.

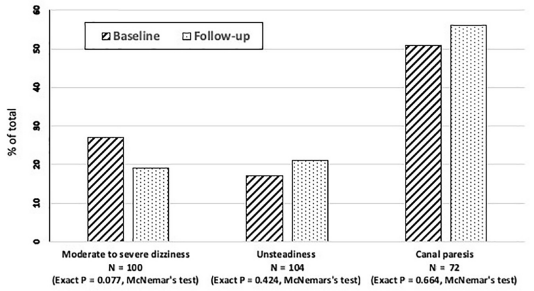

Figure 2. Proportions with moderate to severe dizziness, unsteadiness, and canal paresis at baseline and follow-up.

Data at baseline were compared with data from the last clinical control. McNemar's test for paired data (chi-square and exact *P* values) and paired *t* tests were used. *P* values $<.05$ were considered significant.

Results

Out of 433 patients screened at baseline, 223 were selected for wait-and-scan management. Of these, 114 remained untreated by August 2018 and were included in the study (**Figure 1**). The mean age was 59 years (range, 31-78 years; SD, 10 years), and 62% of the patients were women. The median radiologic follow-up was 10.2 years (interquartile range [IQR], 4.5 years). **Figure 2** shows the proportions of patients with dizziness, unsteadiness, and canal paresis from baseline to follow-up. **Table 1** shows changes in the number of patients with dizziness, unsteadiness, and canal paresis from baseline to follow-up.

Dizziness

The distribution of VAS score at baseline is shown in **Figure 3**.

Moderate to severe dizziness was reported by 27% (n = 27) at baseline and 19% (n = 19) at follow-up. There was no significant change in the proportion with dizziness from baseline until last follow-up. Median follow-up time for the VAS scores was 3.1 years (IQR, 3.1 years).

Posturography

Static posturography was used for 64 patients and dynamic posturography for 40 patients. Seventeen percent (n = 18) were unsteady at baseline and 21% (n = 22) at last follow-up. There was no significant change in the proportion with unsteadiness from baseline until last follow-up, also in analysis of the static and dynamic posturography platforms separately. Median follow-up time was 9.1 years (IQR, 6.6 years).

Table 2. Time Course of Dizziness at Baseline and Follow-up in 98 Patients with Vestibular Schwannoma.[a]

	Baseline		Follow-up[b]	
	n	%	n	%
Attacks	15	15	17	17
Periods	33	34	30	31
Constant	7	7	9	9
No dizziness	43	44	42	43

[a]Reported dizziness last 3 months.
[b]Mean, 3.5 years.

Table 3. Dizziness Characteristic at Baseline and Follow-up in 91 Patients with Vestibular Schwannoma.[a]

	Baseline		Follow-up[b]	
Type of Dizziness	n	%	n	%
Spinning	20	22	14	15
Rocking	22	24	23	25
Walking on pillows	5	6	8	9
Other	1	1	5	6
No dizziness	43	47	41	45

[a]Reported dizziness last 3 months.
[b]Mean, 3.4 years.

Caloric Testing

Caloric testing was included into the testing protocol from June 2003. Fifty-one percent (n = 37) of the patients had canal paresis at baseline and 56% (n = 40) on the last clinical control. There was no significant change in the proportion of patients with canal paresis from baseline until last follow-up. Median follow-up time was 9.1 years (IQR, 6.3 years).

Tumor Volume

In total, 114 patients had radiologic follow-up with at least 2 MRI scans with measurements of tumor volume. Median tumor volume was 139 mm^3 (IQR, 314 mm^3) at baseline and 139 mm^3 (IQR, 288 mm^3) at last follow-up. Median follow-up time was 10.2 years (IQR, 4.5 years). Mean tumor volume did not change significantly during follow-up ($P = .446$, paired t test).

The time course and characteristics of dizziness are shown in **Tables 2** and **3**. Only 7% reported constant dizziness at baseline and 9% after a median follow-up of 3.5 years.

Discussion

This study found no significant changes in dizziness symptoms, postural balance, or caloric response during long-term conservative management of vestibular schwannoma. To our knowledge, this is the first study to investigate long-term development of objective balance and caloric function in patients with untreated vestibular schwannoma.

The findings indicate a good prognosis in this patient group. In a normal population, the proportion of subjects experiencing dizziness and imbalance tends to increase over time due to aging and age-related diseases. Du Pasquier et al estimated postural stability impairment due to aging,[24] and Saman et al measured postural stability in patients with untreated vestibular schwannoma using functional gait assessment scores and found a correlation between age >60 years and decreased postural stability.[25] Breivik et al did not find a significant change in VAS score from baseline to last follow-up but a significant decrease in number of patients with vertigo.[16] Godefroy et al[17] observed 41 patients with vestibular schwannoma with a mean follow-up of 47 months. Some of the patients who reported vertigo or unsteadiness were better at follow-up, and some were worse. No trends were reported.

We found that the function of the vestibular nerve as measured by caloric asymmetry did not seem to deteriorate over time as long as there was no tumor growth. This is in contrast to what was found when long-term hearing outcomes were evaluated in patients with untreated vestibular schwannoma. Several studies have investigated hearing outcome in treated and untreated vestibular schwannomas[26] and found that hearing deteriorates even if the tumor is not treated,[16,27,28] but there is a lack of studies investigating changes in vestibular nerve function during conservative management and how it affects symptoms such as vertigo and imbalance.

In our study, postural unsteadiness was present in 17% at baseline and 21% at last follow-up. This is less than that reported by others. Collins et al[29] found that 49% of patients with vestibular schwannoma had abnormal path lengths with eyes closed prior to surgery. Matthies and Samii tested balance with eyes closed and found abnormal results to be most common in patients with tumors compromising the brain stem but almost equally (41%) in purely intrameatal tumors.[4]

Gerosa et al[30] found that 62% of patients had abnormal results on computerized static stabilometry before GKR. Indications for surgery might include larger tumors, growing tumors, or more symptoms, including dizziness and postural imbalance. In addition, preoperative patients may have increased postural sway due to nervousness. In a previous study, we found that sway on the dynamic platform was associated with tumor size as well as subjective dizziness.[14] In our study, patients had predominantly small tumors without tumor growth. Different prevalence of abnormal postural sway might also result from different choices of normative values. For static posturography, we used normative values from a previously published study with the same platform to measure the balance of healthy controls with a mean age of 52 years, slightly younger than that in the present study. For dynamic posturography, we used normative values integrated in the software supplied by the producer.

In this study, canal paresis was present in 51% of cases at baseline and 56% at follow-up. Humphriss et al reported that 63% of their cases had unilateral canal paresis,[7] and in a group of patients selected for operation, 86% had canal paresis defined as unilateral weakness >20%.[31]

Strengths and Limitations

To our knowledge, caloric function and posturography have not been measured in a long-term follow-up study of untreated vestibular schwannoma patients before, and longitudinal data on subjective vertigo are limited. The observation period in this study was relatively long, with 10-year median radiologic follow-up.

A limitation is the use of 2 methods of posturography since they measure balance in different ways. However, for each patient, the same method was used at baseline and follow-up. This means that a change in measured postural sway would never be due to a change of method. Nevertheless, we did perform a separate analysis of the 2 platforms and found no change in postural sway during follow-up in either of them. Since the focus of this study was change during follow-up, we believe that the use of 2 platforms was of no consequence to the conclusions. The VAS is not a validated method for quantifying dizziness, and the Dizziness Handicap Inventory might have been used to advantage. However, the distribution of VAS scores (**Figure 3**) in our study is quite similar to the distribution of Dizziness Handicap Inventory scores in the study from Humphriss et al[32] and Lloyd et al,[3] indicating that the proportion of patients with moderate to severe symptoms might be comparable.

In this study, only the caloric test was used as an indicator of vestibular nerve function, because this was the only method available to us at the time of inclusion. Adding other tests, such as vestibular evoked myogenic potentials and video head impulse tests, could result in a higher detection of patients with impaired function of the vestibular nerve, particularly the inferior ramus. However, a change in function would normally have been detected since the same method was used throughout the follow-up period. Moreover, the caloric test has proven to be quite sensitive, since in a previous study,[14] 93% of patients with tumors >20 mm were found to have canal paresis >25%.

The most likely explanation for the findings in this study is that central compensation leads to a slight decrease in dizziness over time in patients with newly diagnosed vestibular schwannomas and that this, to some degree, counteracts the effects of aging. Prerequisites for effective central compensation may be a nongrowing tumor and stable peripheral vestibular function.

The clinical significance of this finding is that patients may be reassured that the prognosis is relatively favorable with regard to vestibular symptoms during wait-and-scan management of a nongrowing tumor. Symptoms are likely to remain stable or even decrease slightly over time. Vestibular rehabilitation[33] may be indicated to promote central compensation and improve physical function as well as quality of life in patients with significant residual symptoms.

Summary

This study found no significant change in the prevalence of moderate to severe dizziness, postural instability, or canal paresis during long-term follow-up of conservatively managed cases of vestibular schwannoma.

Author Contributions

Kathrin Skorpa Nilsen, substantial contribution to conception and design of the study, analysis and interpretation of the data; drafting and revising the manuscript for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work; **Morten Lund-Johansen**, substantial contribution to conception and design of the study, analysis and interpretation of the data; drafting and revising the manuscript for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work; **Stein Helge Glad Nordahl**, substantial contribution to conception and design of the study, analysis and interpretation of the data; drafting and revising the manuscript for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work; **Monica Finnkirk**, substantial contribution to conception and design of the study, analysis and interpretation of the data; drafting and revising the manuscript for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work; **Frederik Kragerud Goplen**, substantial contribution to conception and design of the study, analysis and interpretation of the data; drafting and revising the manuscript for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work.

Disclosures

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III

Postural Sway Predicts Growth in Untreated Vestibular Schwannoma: A Retrospective Volumetric Study

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ABSTRACT

Background: One in three vestibular schwannomas (VS) will grow within three years after diagnosis, but no reliable baseline parameter has been found to predict such growth.

Objective: To determine if postural sway is associated with growth of untreated VS.

Methods: Patients with newly diagnosed sporadic VS assigned to a wait-and-scan protocol were identified from a prospectively maintained database. Postural sway was measured by posturography at baseline and patients were classified as steady or unsteady. Observer-blinded volumetric tumor measurements were performed on the diagnostic MRI and a 3-year control MRI. Tumor growth quantified as relative growth (%) and volume-doubling time (VDT and VDT^{-1}) were investigated as dependent variables against baseline parameters.

Results: Out of 204 VS patients, 53 (26%) were classified as unsteady on the platform at baseline. Median tumor volume was 0.32 cm^3 (range 0.02-4.79), and 51% demonstrated significant growth within three years. Unsteady patients had significantly faster-growing tumors, with a mean relative growth of 172.5% compared to 79.5% in steady patients ($p<.006$). Seventy-seven percent of unsteady patients had >20% volume increase, compared to 42% in steady patients ($p<.001$). Mean VDT^{-1} was 0.65 doublings per year for unsteady patients, and 0.22 for steady patients ($p<.001$). Multivariate regression analysis including demographic and clinical parameters showed an OR of 5.6 (95% CI 2.6,11.8) for growth in unsteady patients.

Conclusions: This is the first demonstrated association between a measurable parameter and future growth in untreated VS. Our findings may help clinicians identify patients with a higher risk for tumor growth and provide closer monitoring or early treatment.

ABBREVIATIONS

CISS Constructive Interference Steady State

COP Center of Pressure

MRI Magnetic Resonance Imaging

MS Microsurgery

PTA Pure Tone Average

SRS Stereotactic Radiosurgery

VDT Volume-doubling Time

VS Vestibular schwannoma

INTRODUCTION

Vestibular schwannomas (VS) are benign and usually slow-growing neoplasms arising from the vestibulocochlear nerve (1). The most common symptoms of VS are progressive hearing loss, tinnitus, dizziness, and unsteadiness (2,3). Most cases present with smaller tumors, which are often followed with annual MRI and treated only if evidence of growth (4,5). The proportion of growing tumors varies in the literature (6,7). A recent review reported that approximately one in three tumors grow within three years, and fifty percent within the first five years (8). To date, no parameter is identified to reliably predict tumor growth (8). Studies have described associations between clinical variables and tumor growth, but these have not been confirmed.

In a recent review of altogether 32 studies encompassing 4201 patients, Paldor et al. concluded that patient-reported imbalance was the only clinical parameter that demonstrated a possible association with growth (8). Two out of three articles pointed to an association, whereas the third was negative (9-11). For the other parameters (age, sex, hearing loss, tinnitus, vertigo, initial tumor size, tumor location, and tumor side) studies were contradictory (5,7,10-13). In their review, Paldor et al. called for future reports on the significance of imbalance in predicting tumor growth.

Previous studies have been limited to analyzing patient-reported imbalance. The present study aimed to determine if a measurable parameter, namely postural sway, is associated with volumetric growth of untreated vestibular schwannomas within 3 years. Possible confounders were examined utilizing multivariate regression analysis. The null hypothesis was that there would be no association between postural sway measured at diagnosis and tumor growth within the following three years.

METHODS

Study design

This is a retrospective cohort study on subjects from a prospectively maintained database of consecutive VS patients referred to a single institution. The null hypothesis and statistical analysis plans were established *a priori* to data extraction. One researcher (DD), who was blinded to posturography data, performed all tumor volume measurements. The following covariates were examined by means of multivariate regression analysis: age, gender, pure-tone hearing thresholds, tinnitus, subjective unsteadiness, dizziness, and initial tumor volume. The acoustic neuroma database was approved by the Ethical Committee in 2001 (REK114/01). Informed consent to collect and analyze data was obtained from all patients when enrolled.

Setting and patients

Our hospital is responsible for treating all patients with vestibular schwannomas within a catchment area of approx. 5 million people. All newly referred VS patients between 2000 and 2011 were included in a database for annual follow-up over five years and then 10 years from baseline. For this study, patients assigned to initial wait-and-scan management were included. Patients with bilateral VS, patients missing clinical or balance platform data and patients with suboptimal MRI quality, were excluded.

Clinical data

The presence or absence of dizziness, unsteadiness, and tinnitus was recorded by the examining physician on each visit. The patients also underwent pure tone audiometry, and pure tone average (PTA) was calculated as the average hearing threshold in dB_{HL} at 0.5, 1, 2 and 3 kHz. In addition, patients were routinely investigated by posturography, and the data were similarly prospectively recorded (4,14). A majority of the patients underwent bithermal caloric testing with irrigation of each ear canal at 30 and 44 degrees centigrade, and canal paresis was defined as a caloric asymmetry >25 % according to Jongkees' formula (15).

Static and dynamic posturography

A static posturography platform was used initially *(n = 124)*. However, this was replaced in 2006 by a dynamic platform *(n = 80)*. In order to reconcile the differences in testing conditions and sway parameters from these two platforms, results were dichotomized (steady/unsteady) based on previously established normative data (17).

Static posturography was performed on a force platform containing three pressure transducers (Cosmogamma, Bologna, Italy). The patient was asked to stand quietly on the platform for 60 seconds with eyes open, then for 60 seconds with eyes closed. A computer sampled data from the pressure transducers at a frequency of 10 Hz and calculated the center of pressure (COP) exerted by the patient on the platform. The path length in millimeters described by the COP with the eyes closed was used for analysis. Based on a previously published study with normative data from healthy individuals with a mean age of 52 years, a path length > 1600 mm defined the patient as unsteady (17).

Dynamic posturography was performed using the EquiTest (NeuroCom, Pleasanton, California) and the Sensory Organization Test protocol (16). This test results in a composite score, which is a weighted average of the equilibrium score (ES) in 6 different sensory conditions: (1) eyes open, (2) eyes closed, (3) eyes open with sway referenced visual surroundings, (4) eyes open with sway referenced platform, (5) eyes closed with sway referenced platform and (6) eyes open with sway referenced visual surroundings and platform. Unsteadiness was defined as a composite score lower than the normative values integrated with the software supplied by the producer.

Volumetric assessment

The diagnostic MRI and the routine 3-year follow-up scan were reviewed for each patient. For patients who received interventional treatment within three years, the pretreatment MRI was obtained. Preferably T1-weighted MRI with gadolinium contrast was selected. If not available, CISS sequences were analyzed.

A total of 408 MRI scans were retrieved and assessed. Volumetry were performed on iPlan Brainlab Elements (Version 2.4.0, Brainlab AG, Munich, Germany). We used the Smartbrush®

function, which provides an instant method for outlining the tumor on each image slice **(Fig. 1)**. A software algorithm reconstructed a 3-dimensional object based on the selected areas and presented a detailed report including object volume in cubic centimeters (cm^3). The time required to create a 3-dimensional model of the tumor and extract volumetric measurements was typically 5-10 minutes.

For 38 patients (18,6%), volumetric measurements on Brainlab were not possible due to old MRI format. For these cases, the volume was calculated using the following formula:

$$V = \frac{4}{3}r^3 = \frac{4}{3}\left(\frac{x}{2}\right)\left(\frac{y}{2}\right)\left(\frac{z}{2}\right) = \frac{xyz}{6}$$

Growth analysis

In accordance with recent studies, an increase of tumor volume ≥ 20 % was considered to represent significant growth outside the margin of error (18-21). Volume-doubling time (VDT) was calculated using the following formula:

$$VDT = \frac{\ln 2 \ (t_2 - t_1)}{\ln \frac{v_2}{v_1}}$$

The VDT describes the growth in terms of an exponential model (7,22,23). A VDT that tends towards positive or negative infinity implies a stationary tumor, while a VDT close to zero implies a tumor growing or shrinking rapidly. For statistical analyses, we therefore instead used the reciprocal value, denoted as VDT^{-1} (number of doublings per year). VDT^{-1} increases with growth rate and a negative VDT^{-1} implies tumor shrinkage, thus facilitating conventional statistical analysis.

Statistical analysis

Continuous features are presented with means, medians, ranges, and standard deviations. Age was categorized in intervals based on percentiles (25, 50 and 75) and dichotomized at the 75-percentile. Continuous and categorical variables were compared between groups by independent

sample T-test and Pearson's chi-squared test. To assess the relationship between tumor growth and baseline parameters, variables with p-values ≤ 0,1 in univariate analysis were included in a stepwise backward-selection multivariate analysis until only significant factors ≤ 0.05 remained. Canal paresis was not included as a predictor in the multivariate analysis due to missing data for a large proportion of the subjects (n = 71). However, due to its relevance, it was included in the univariate analysis. Two-sided p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using Stata Software (Version 16.0 StataCorp) and IBM SPSS Statistics (Version 25.0).

RESULTS

Demographic data

Out of 433 patients, 223 had been assigned to a wait-and-scan protocol. Nineteen patients were excluded due to conversion to surgical treatment without subsequent MRI (n = 6), missing clinical or platform data (n = 6), poor MRI quality (n = 4), radiosurgery within 6 months of observation (n = 2), and bilateral tumor (n =1). A total of 204 patients were included.

Baseline data are presented in **Table 1**. Fifty-three patients (26.0%) were classified as unsteady by posturography. Within three years, 70.1% of patients remained in the wait-and-scan protocol, while 24.0% and 5.9% received stereotactic radiosurgery and microsurgery, respectively. The mean follow-up time was 2.3 years (0.5 – 3.7). The median tumor volume was 0.319 cm^3 at baseline, and 0.490 cm^3at follow-up. Half of the tumors (51.0%) grew >20% during the period of observation. Mean volume-doubling time (VDT) was 4.01 years, and mean VDT^{-1} was 0.33 volume-doublings per year.

Descriptive data

There were no significant differences in baseline age, gender or tumor volume between steady and unsteady patients **(Table 2)**. However, at follow-up, unsteady patients had significantly larger tumor volumes than steady patients ($p = .002$) **(Fig. 2).** Mean VDT^{-1} was 0.65 and 0.22 doublings per year for unsteady and steady patients, respectively ($p < .001$) **(Fig. 3).** Unsteady patients had significantly faster-growing tumors, with a mean relative growth of 172.5% compared to 79.5% in steady patients ($p<.006$). A volume increase >20% was found in 41 of 53 unsteady patients (77%), and 63 of 151 of steady (42%) ($p < 0.001$). None of the tumors in unsteady patients showed shrinkage by 20% or more, which was evident in 17% of the steady patients **(Fig. 4)**. Radiosurgery or microsurgery was given to 52.8% and 21.9% of unsteady and steady patients, respectively ($p < .001$). Unsteadiness as a diagnostic test for growth has a sensitivity at 40.0%, specificity at 87.1%, positive predictive value at 76.4% and negative predictive value at 58.3%.

Regression analysis

In the unadjusted (univariable) analysis, linear associations with growth (VDT^{-1}) were found for both subjective and objective unsteadiness, dizziness, and age >64 years (negative association **(Table 3**). However, on the adjusted analysis, only unsteadiness based on posturography and age >64 years (negative) remained significant predictors of growth. When performing multiple logistic regression analyses, the same predictors were revealed for relative growth >20%. Unsteady patients had five times higher odds for significant volumetric tumor growth (OR = 5.56) **(Table 4)**.

DISCUSSION

Main findings and previous knowledge

We found that tumors in VS patients grew significantly faster if the patient was unsteady on the platform. Unsteady patients had five times higher odds for significant tumor growth. These are new findings. We also confirmed that a patient-reported history of unsteadiness may associate with growth, although this finding has not been consistent in previous reports (9-11,24).

Unsteady patients are often inconsistent when characterizing their complaint, changing their description when asked again only 30 minutes later (25). The threshold for reporting unsteadiness may also vary between patients depending on their expectations, symptom intensity, timing, as well as on personality and emotional factors. VS patients in their fifties or sixties often feel that their balance has become poorer, but may fail to report it as a symptom. Thus, postural instability is a more reliable indicator of imbalance. Posturography is a non-invasive and fast method for measuring postural sway in a clinical setting. Today, commercially available force platforms can be combined with open-source software to provide a posturographic system. However, the sensitivity and specificity of such platforms with regards to vestibular dysfunction are likely to vary depending on test protocols (conditions) as well as test parameters, e.g. sway speed or area. Based on a previous study, condition 5 of the Sensory Organization Test, seems to correlate better (compared to static conditions) with tumor size and canal paresis in patients with vestibular schwannoma (16,17).

Recent studies have shown volumetric tumor measurements to be the most sensitive parameter for detecting size changes in VS (18,19,21,26). Measuring tumor volume and calculating VDT is fast, simple and credible using modern radiology software. In this study, the observer was blinded for clinical information, thus reducing bias when measuring tumor volumes. There is no consensus on how to define VS growth, but recent studies define a threshold of 20% volume increase (18-21). In 2010, we established volume-doubling time (VDT) as the most reliable measure of VS growth (7,22).

Interpretations of the association between unsteadiness and tumor growth

Our findings may be explained by the interplay of two critical determinants of postural instability in unilateral vestibular disorders, namely peripheral vestibulopathy and central compensation. A previous study from our group found that functional damage to the vestibular nerve is usually detectable in VS patients at an early stage of tumor development - while the tumor is relatively small (16). Nevertheless, approximately one-third of patients do not report dizziness or unsteadiness. Moreover, larger tumors do not seem to be associated with more dizziness (16) or increased postural sway (present study). Another study from our group showed that the long-term prognosis in VS patients is favorable with respect to dizziness symptoms when the tumor does not grow after diagnosis (27). This is explained by central compensation, which is a powerful mechanism reducing or even eliminating vertigo symptoms in most VS patients. However, the present findings may indicate that central compensation is less complete in patients with a growing vestibular schwannoma. A stationary tumor may allow enough time for central compensation to take place and thereby cause less postural imbalance, while a growing tumor may cause progressive peripheral vestibulopathy with less time for central compensation and more postural imbalance. We hypothesize that it is the rate of change, more than the absolute degree of, peripheral vestibulopathy that determines postural instability.

Other potential predictors of tumor growth

Although unsteady patients had slightly larger tumors at first MRI ($p = .155$), initial tumor volume was not found to be a predictor of later growth in either univariate nor multivariate analysis. This corresponds to the review by Paldor et al., where 13 of 20 articles did not find a correlation between initial tumor size and later growth (8).

Hearing level, as measured by pure tone average, was not a predictor of tumor growth, and previous studies have found only a weak relationship between tumor size and audiometric results (16). This could be due to the fact that hearing loss is believed to be caused indirectly because of pressure from the tumor on the cochlear nerve. This pressure depends to a great degree on the localization and not merely on the size of the tumor. In contrast, tumor growth occurs within the vestibular nerve itself, and vestibular nerve damage may therefore be a more consistent feature of tumor growth regardless of localization.

Vertigo was in our study found to be a predictor in the univariate analysis, but the effect disappeared in the multivariate analysis. This could be due to collinearity. However, the finding is in agreement with previous studies which have failed to identify vertigo as a predictor of growth (7,11,13). This could be due to the subjective and multifactorial nature of vertigo and dizziness.

The presence of caloric asymmetry was not a predictor of tumor growth. The predictive value of caloric asymmetry with respect to growth may be decreased by the fact that 72 % of VS patients already have this finding at the time of diagnosis (16). Canal paresis seems to take place at an early stage of the disease while the tumor is relatively small. The same reasoning could possibly explain the negative findings with respect to hearing loss and tinnitus, which is present in 94 % and 83 % of patients respectively at the time of diagnosis (28).

Age > 64 years was found to be a negative predictor of tumor growth within 3 years. The vast majority of previous studies as summarized in the review by Paldor et al., do not find an association between age and tumor growth (8). More active treatment may still be indicated in younger patients because they require longer follow-up.

Study strengths and limitations

Among the strengths of the study are the relatively large number of consecutively enrolled patients and the highly significant results. The cohort was closely monitored, and very few patients were lost to follow-up. Moreover, the study used observer-blinded volumetric assessment and *a priori* defined growth criteria.

The retrospective design is a limitation, although the null hypothesis and statistical analysis protocol were determined before data extraction and tumor measurements. Another limitation is the use of two different posturography platforms, which may limit the generalizability of the results. However, unsteadiness predicted tumor growth when we analyzed the dynamic and static posturography platforms separately (not shown). At our center, VS patients that have undergone testing on both platforms show highly significant correlations between path length with eyes

closed on the static platform and the composite score on the dynamic platform (unpublished data).

Based on our findings, the predictive value of the caloric test with regards to prospective tumor growth is probably limited. However, the results must be interpreted with caution since the caloric test was only performed on approximately 2/3 of the patients. The missing caloric tests were due to capacity limitations at the vestibular laboratory, and we consider this to be a low risk of bias (missing-at-random).

Impact on patient care

Tumor growth is the main factor determining treatment, and our findings suggests that patients who show postural instability have a higher risk of growth, requiring either treatment or close follow-up. Our results indicate that postural sway is better at confirming risk for tumor growth (adequate specificity) than detecting it (low sensitivity). Therefore, posturography should in no case be considered a substitute for serial MRI.

CONCLUSION

Objective postural instability measured by posturography was found to associate strongly with volumetric tumor growth within 3 years in patients with untreated vestibular schwannoma. This is the first proven association between a measurable parameter and later growth of a vestibular schwannoma.

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Figure 1: The Smartbrush® function iPlan Brainlab Elements provide an interactive method for 3D object creation by outlining an area on each image slice.

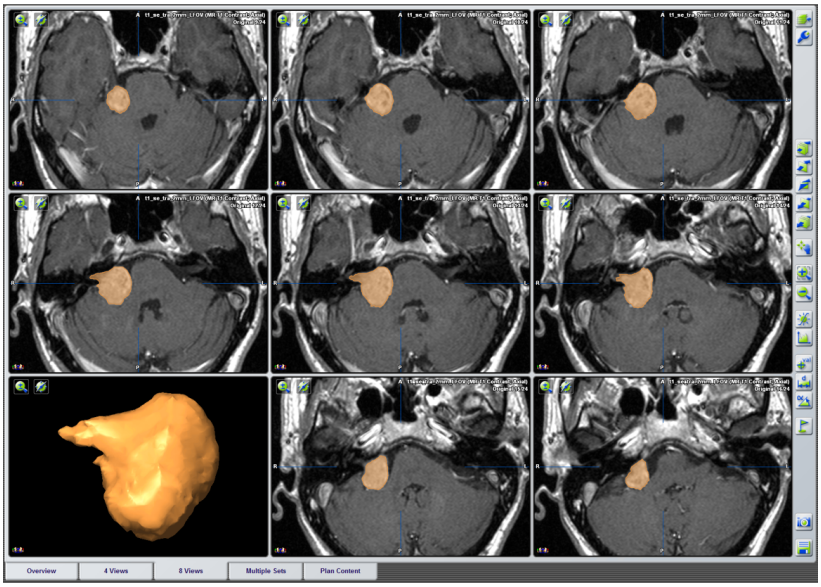

Figure 2: The scatterplot represents each tumor volume at diagnostic MRI and at control MRI. Regressions lines illustrates the trend for unsteady and steady patients. Presented volumes are mean values.

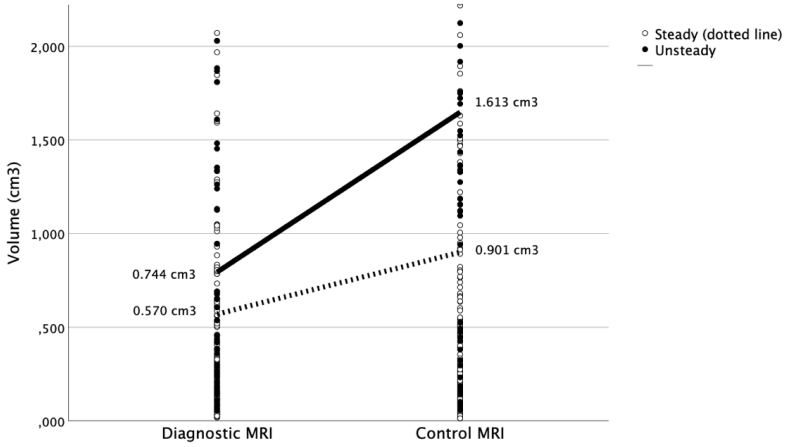

Figure 3: Boxplot illustrating median, range and IQR of VDT^{-1} for steady and unsteady patients in a logarithmic scale.

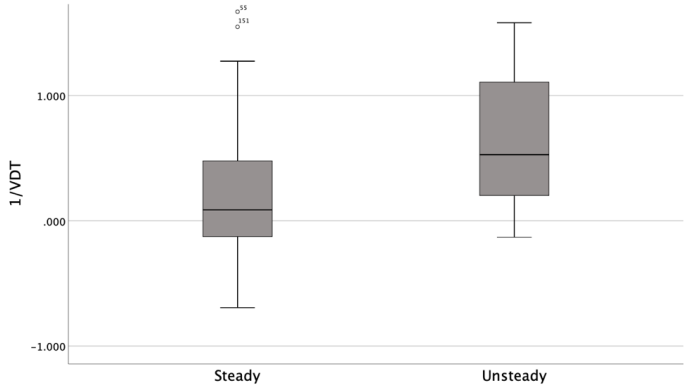

Figure 4: Proportion of significant growth and regression in unsteady and steady patients.

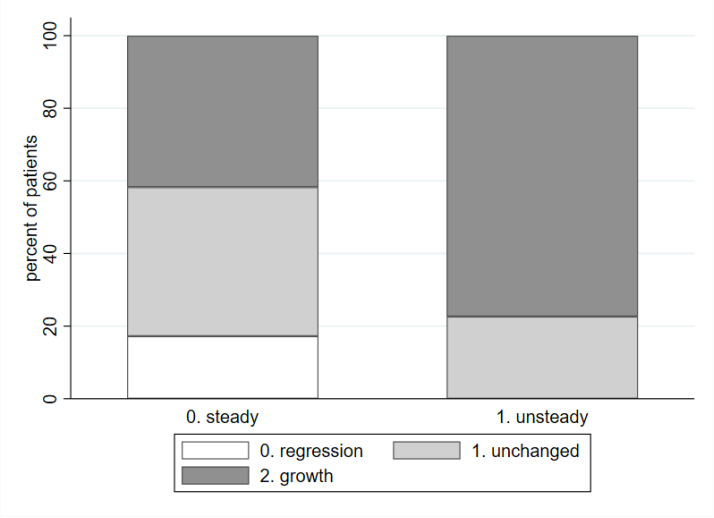

TABLE 1. Population description

Number of patients	204
Gender, n (%) female	113 (55.4)
Age at diagnosis, mean (range)	56.8 (29.0, 81.0)
Unsteady based on posturography, n (%) yes	53 (26.0)
Treatment within 3 years after inclusion	
Continued observation, n (%)	143 (70.1)
Stereotactic Radiosurgery, n (%)	49 (24.0)
Microsurgery, n (%)	12 (5.9)
Follow-up, years, mean (range)	2.3 (0.5, 3.7)
Volume at diagnosis (cm^3), median (range)	0.319 (0.017, 4.790)
Volume at last control (cm^3), median (range)	0.490 (0.013, 8.013)
Relative growth >20%, n (%)	104 (51.0)
VDT (volume doubling time, in years), mean (SD)	4.01 (-227.50, 175.43)
VDT^{-1} (volume doublings per year), mean (SD)	0.33 (-0.62, 2.18)

TABLE 2. Descriptive data for VS patients classified as unsteady or steady based on platform posturography

	Unsteady VS patients (n = 53)	Steady VS patients (n = 151)	p Value	Cohen's d
Age at diagnosis (y), mean (SD)	59.0 (11.1)	56.0 (10.5)	0.073†	0.29
Gender, n (%) female	32 (60.4)	81 (53.6)	0.396††	
Volume at diagnosis (cm^3), mean (SD)	0.744 (0.730)	0.570 (0.782)	0.155†	0.23
Volume at follow-up (cm^3), mean (SD)	1.613 (1.563)	0.901 (1.325)	0.002†*	0.51
VDT^{-1}, mean (SD)	0.65 (0.60)	0.22 (0.47)	<0.001††*	0.85
Relative growth (%), mean (SD)	172.49 (228.51)	79.54 (200,20)	0.006†*	0.45
Volume increase >20%, n (%) yes	41 (77)	63 (42)	<0.001††*	
Volume shrinkage >20%, n (%) yes	0 (0)	26 (17)	<0.001††*	
Active treatment first 3 years, n (%) yes	28 (52.8)	33 (21.9)	<0.001††*	

* $p < 0.05$, † Independent samples T-test, †† Pearson's Chi-squared Test

n = number of patients, SD = standard deviation, VDT = volume-doubling time, y = years,

TABLE 3. Linear regression analysis of baseline predictors of tumor growth (VDT^{-1})

Variable	Observations	Coefficient	CI	p Value
Univariate				
Age (y)	204	-0.003	-0.010, 0.003	0.323
Age > 64 y	204	-0.236	-0.405, -0.066	0.007*
Sex (female)	204	-0.039	-0.189, 0.111	0.605
Unsteady (posturography)	204	0.432	0.272, 0.591	<0.001*
Unsteady (history)	204	0.285	0.134, 0.436	<0.001*
Initial tumor size (cm^3)	204	-0.010	-0.107, 0.087	0.835
Hearing level (PTA)	200	-0.001	-0.004, 0.002	0.477
Canal paresis > 25%	133	0.111	-0.072, 0.294	0.233
Dizzy (history)	203	0.204	0.057, 0.352	0.007*
Tinnitus (history)	203	0.057	-0.113, 0.228	0.509
Multivariate				
Age > 64 y	204	-0.281	-0.438, -0.123	0.001*
Unsteady (posturography)	204	0.458	0.303, 0.614	<0.001*

* $p < 0.05$

CI = confidence interval, PTA = pure-tone average, VDT = volume doubling time, y = years

TABLE 4. Logistic regression analysis of baseline predictors of tumor growth (relative growth >20%)

Variable	Observations	Odds ratio	95% CI	p Value
Univariable				
Age interval (y)	204			
<50.5 **				
50.5-57.0		0.85	0.39, 1.86	0.691
57.1-63.7		0.92	0.42, 2.02	0.842
>63.7		0.49	0.22, 1.08	0.076
Sex (female)	204	0.75	0.43, 1.31	0.310
Unsteady (posturography)	204	4.77	2.32, 9.81	<0.001*
Unsteady (history)	204	1.80	1.00, 3.21	0.048*
Tumor size (cm3)	204	0.82	0.57, 1.18	0.290
Hearing level (PTA)	200	1.00	0.99, 1.01	0.520
Canal paresis > 25%	133	1.95	0.97, 3.95	0.061
Dizzy (history)	203	1.72	0.99, 3.01	0.056
Tinnitus (history)	203	1.58	0.84, 2.98	0.160
Multivariable				
Unsteady (posturography)	204	5.56	2.62, 11.80	<0.001*
Age interval (y)	204			
<50.5 (reference category)				
50.5-57.0		0.87	0.38, 1.97	0.732
57.1-63.7		0.98	0.43, 2.22	0.953
>63.7		0.38	0.16, 0.90	0.028*

* $p < 0.05$

** reference category

CI = confidence interval, PTA = pure-tone average, y = years

IV

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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

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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**.

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.

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.

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 vestibular test	Sensitivity[a] (%)	% abnormal results related to tumor side		
		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]

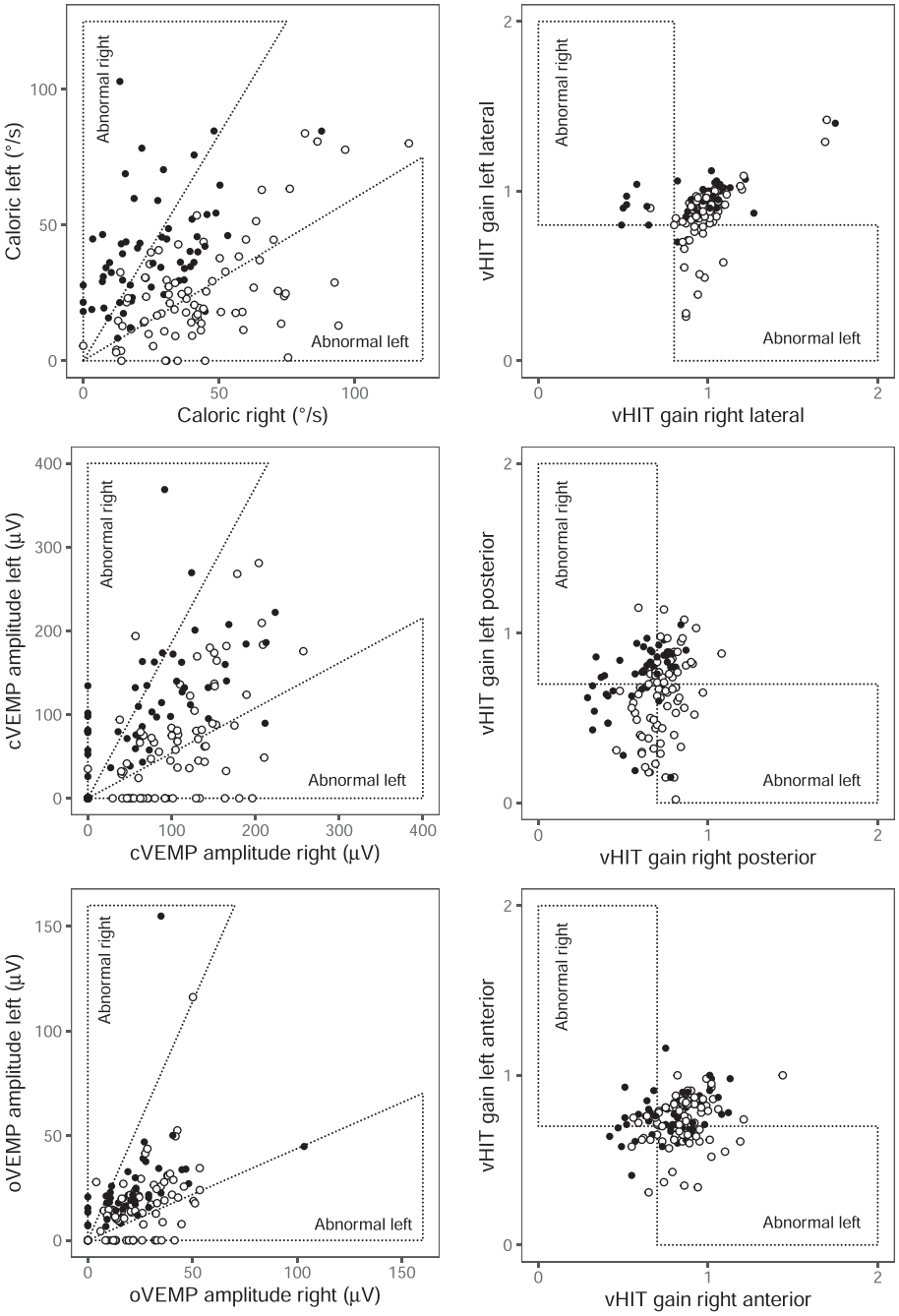

Figure 1. Vestibular test results in 137 patients with untreated small to medium-sized vestibular schwannoma. Black and white dots indicate patients with right- and left-sided tumors, respectively. Dotted areas indicate abnormal results defined as asymmetry greater than 25%, 30%, and 39% for caloric 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.

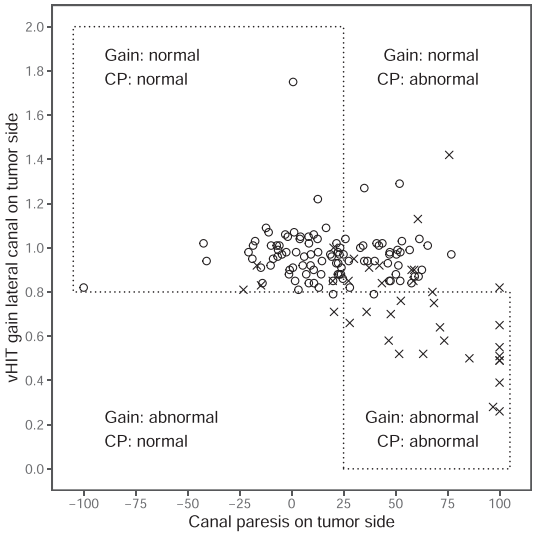

Figure 2. Scatterplot showing the relationship between vHIT lateral canal gain and canal paresis on the tumor side in 137 untreated VS patients. CP, canal paresis; Cross, with catch-up saccades; dots, without catch-up saccades; vHIT, video head impulse test; VS, vestibular schwannoma.

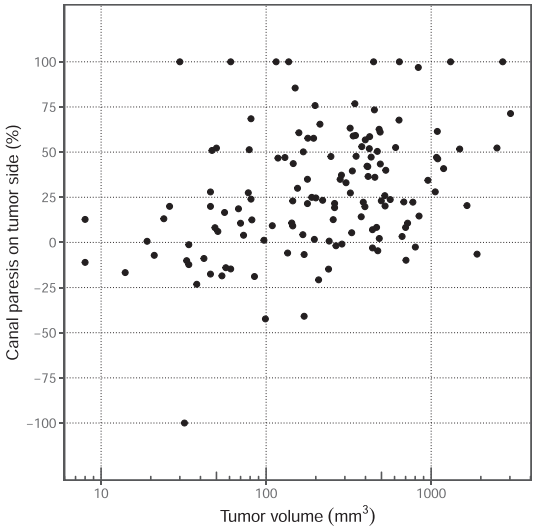

Figure 3. Scatterplot showing the relationship between caloric asymmetry on the tumor side (%) and markings of tumor volume (mm^3) on a logarithmic scale.

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.

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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.

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