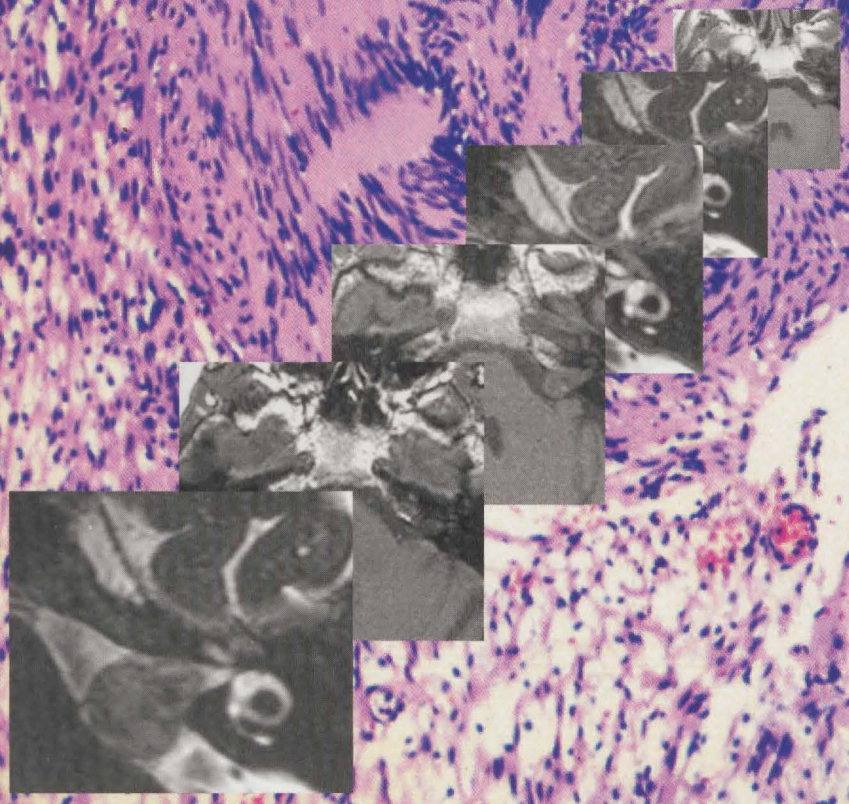
# VESTIBULAR SCHWANNOMAS

## ASPECTS OF BIOLOGICAL BEHAVIOR





ERNESTINE M. STIPKOVITS

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# VESTIBULAR SCHWANNOMAS
## ASPECTS OF BIOLOGICAL BEHAVIOR

Het vestibulair schwannoom: aspecten van biologisch gedrag
(met een samenvatting in het Nederlands)

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*Voor ma*

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# 1

# CHAPTER 1

## GENERAL INTRODUCTION

## INTRODUCTION

A vestibular schwannoma (VS) is a benign tumor that arises from the superior or inferior part of the vestibular portion of the eighth cranial nerve. A VS usually originates in the internal auditory canal; from there, it might expand into the cerebellopontine angle and posterior fossa. This kind of tumor was first described in 1777 by Sandifort, in a post-mortem study (1). His publication was followed by several other case reports, each with a different histological diagnosis (2-5). Verocay (1910) called the tumor a 'neuroma', since he found parallel fibers that he considered to be axons (6). Furthermore, he discovered certain histological structures that came to be known as 'Verocay bodies'. Antoni (1920) found two different kinds of cell within the tumor: type A and type B cells (7). He thought the tumor originated in the embryological Schwann cell. The study by Murray and Stout (1942) provided irrefutable evidence that the tumor does indeed originate there (8). Since then, this view has been generally accepted. The correct nomenclature is thus 'vestibular schwannoma'. However, the term acoustic neuroma is still widely used, since hearing loss is usually the first and predominant symptom.

At the beginning of the 20th century, the diagnostic tools were very limited. Thus, only large tumors could be detected. Their presence was usually ascertained when they gave rise to neurological symptoms. Cushing distinguished seven sequential stages of the disease, the first comprising audiovestibular dysfunction, the last brainstem compression and death (9). Surgical treatment was possible, but operative mortality was high; in 1903, Krause reported it to be 84% (10). In 1917, Cushing reported an operative mortality of 30%; by 1930, that figure had diminished to 4% (9). Due to refinements in surgical techniques - such as the introduction of various surgical approaches, the use of antibiotics, and the introduction of the operating microscope - the rate of operative mortality and morbidity has been reduced considerably.

Gradually, more diagnostic tools became available. After World War II, several audiometric techniques were developed to distinguish between retrocochlear (such as a VS) and cochlear disorders. The first and most sensitive one was the alternating binaural balance test. This test was originally described by Fowler in 1937 (11). It was discovered that the loudness recruitment phenomenon is present in cochlear hearing loss but absent in retrocochlear hearing loss. Later, several other techniques were developed to measure recruitment. One is the Tone Decay Test, which measures perstimulatory tone adaptation (12). In retrocochlear disorders, perstimulatory adaptation is usually severely increased. The third important audiological technique is Von Békésy audiometry (13), as modified by Jerger (14) in 1960. Brainstem evoked response audiometry proved to be the most reliable way to detect a VS (15). This technique became popular after 1970 (16). Caloric testing, as introduced in 1906 by Bárány (17), was used more frequently. The classic Fitzgerald-Hallpike bithermal caloric test is now the generally accepted method (18). Eye movements may be recorded electrically using the technique of electronystagmography. Imaging techniques also improved in the course of time. In 1910, Henschen showed that widening of the internal auditory canal on X-rays was indicative of the presence of a VS (19). Stenvers refined this technique by developing a special plane in 1918 (20). Roentgen tomography and air-cisternography made it feasible to depict the internal auditory canal and the cerebellopontine angle (21). Rademakers (1973), studying a series of 61 operated patients, found that 25 % of the VSs did not lead to changes in the morphology of the petrous bone (22). He concluded that a VS may not always be detected by a Stenvers X-ray or a tomography. However, air-cisternography had a sensitivity of 100% in his material. When computed tomography (CT) was introduced, a 2-cm lesion was the smallest that could be detected. Subsequent generations of CT scanners have been able to detect much smaller tumors. Since the advent of magnetic resonance imaging (MRI) and the use of intravenously administered gadolinium, it has become possible to detect the smallest intra-

canalicular VSs. However, false positives have been reported.

Since MRI became available, a greater number of patients with a VS have been identified. Some of them have minor symptoms or none at all. Understandably, they are reluctant to undergo any treatment. Their situation might call for a policy of conservative management. Other factors may also play a role in the decision to refrain from treatment: the tumor may be in the only hearing ear; the patient may be advanced in age and/or in poor physical condition; or there may be a long history of symptoms prior to the detection of a small tumor.

Several longitudinal studies of conservatively managed patients have shown that in a large percentage of cases, the VS does not grow. In the future, however, longer follow-up periods may show otherwise. To compare the outcome of different studies, it is necessary to have a uniform method of determining the size of the tumor. It is now generally accepted that computer-assisted volume calculations, based on MR imaging, provide the most reliable measures of tumor size. However, this technique requires a small slice thickness, for instance 1 mm, which is still difficult to attain in clinical practice. Therefore, it will be some time before any results of longitudinal studies using this technique become available. Meanwhile, there is a need for a standardized and reliable method to assess the size of a VS.

To select patients for conservative management, a predictive factor of tumor growth is needed. After analyzing the results of 12 large studies, Walsch et al. concluded that such a factor has not yet been found (23). Formerly, it was believed that a VS is a gradually expanding lesion and will eventually pose a threat to the patient's life. Nowadays, there are doubts about this presumed outcome. In the MRI–era, two new classes of VS have been discovered: extremely small lesions and (almost) asymptomatic tumors. Follow-up with regular clinical assessment and serial MRI is currently the only way to assess the symptoms and the growth of the tumor. It remains to be established which factors lead to the audiovestibular symptoms and findings.

## OUTLINE OF THIS THESIS

The overall objective of this study is to gain insight into the biological behavior of VSs. To that end, we have tried to establish the relations between audiovestibular symptoms, on the one hand, and tumor size, tumor growth, and the histological characteristics of the tumor, on the other. A more specific objective is to expand our understanding of tumor growth by analyzing a longitudinal study that was based on serial measurements of tumor size carried out by means of MRI. For that purpose, we tried to develop a measuring technique that is applicable in images derived from different generations of MRI scanners.

*Chapter 2* reports on a study about the hearing of patients with a unilateral VS in relation to the type and duration of symptoms.
*Chapter 3* discusses the relation between tumor size, tumor progression, and findings from vestibular examination.
*Chapter 4* presents a longitudinal study that was conducted in patients who did not undergo therapy. This chapter introduces a new protocol to determine tumor size on MRI and to assess possible changes between consecutive observations.
*Chapter 5* considers whether the presence or absence of vestibular paresis in patients with a VS is related to the histological parameters of the tumor.
*Chapter 6* describes the initial vestibular status and the audiometrical changes through time in three patients with a shrinking tumor.

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# 2

# CHAPTER 2

## PROFILE OF HEARING IN PATIENTS WITH UNILATERAL ACOUSTIC NEUROMAS; THE IMPORTANCE OF THE CONTRALATERAL EAR

E.M. Stipkovits, J.E. van Dijk, K. Graamans

*(The American Journal of Otology 1998;6:834-839)*

## ABSTRACT

**Objective:** The aim of this study was to describe hearing in patients with a unilateral acoustic neuroma in relation to the sort and duration of symptoms.
**Study design:** The study design was a retrospective clinical study.
**Setting:** The study was conducted at a tertiary referral center.
**Patients:** A total of 171 patients with a unilateral acoustic neuroma participated.
**Intervention:** Diagnostic measures were performed.
**Main outcome measures:** The subjective experience of symptoms, a number of audiometric parameters of the affected and the contralateral side, tumor size, and their mutual relations were measured.
**Results:** No significant correlation was found between tumor size and audiometric parameters. Significant correlations could be shown between the duration of hearing loss and thresholds in the pure-tone audiogram, the speech reception threshold, and the maximum discrimination in the speech audiogram. Thresholds in the pure-tone audiogram of the contralateral ear were significantly worse than those of the international standard. A significant difference in age between men and women with unilateral acoustic neuromas was found.
**Conclusions:** Hearing is not worse in patients with larger tumors. The longer the duration of subjective hearing loss, the more severe is hearing impairment. The hearing loss of the contralateral ear might be responsible for the composition of the category of patients in whom an acoustic neuroma is diagnosed effectively. Presumably, demographic features result in an age difference between male and female patients.

## INTRODUCTION

Acoustic neuroma (AN) is the usual name given to a schwannoma of the vestibular part of the eighth cranial nerve. The term AN is used extensively, presumably because of all the symptoms associated with this lesion, hearing loss often is the most predominant. Considerable research has been performed on the audiologic symptoms of ANs. The reports on this subject, however, merely evaluate the results of audiologic tests in the detection of ANs. With modern imaging techniques, in particular magnetic resonance imaging, ANs can be detected with high specificity and sensitivity. Audiometry has lost most of its relevance for this purpose. Nevertheless, we investigated hearing in patients with an AN for three reasons. First, modern imaging techniques have shown a new category of patients, namely those with extremely small, mostly intracanalicular lesions. Moreover, ANs have been shown accidentally in patients who had no audiovestibular symptoms. It generally is accepted that there is no relation between the degree of hearing loss and the size of the tumor (1-7). It is questionable whether this still holds true in the current patient population. Second, it is worthwhile investigating audiologic parameters in relation to the sort and duration of the patient's symptoms. These data might provide insight into the biological activity of the lesion. Third, the literature on the audiologic assessment of patients with an AN hardly mentions the contralateral ear. Yet, hearing on the unaffected side has considerable impact on the morbidity of the patient. Currently, preservation of some hearing may be a realistic goal in the treatment of ANs. One criterion that should be considered is whether the preserved hearing will be of any value to the patient (8-10). In that light, the functional status of the contralateral ear plays a crucial role in determining the benefit of this type of treatment. The aim of the current study is to elucidate the three issues mentioned above in patients with a unilateral AN.

## PATIENTS AND METHODS

Between 1986 and 1996, 230 patients with a tumor in the cerebellopontine angle were referred to the University Hospital Utrecht. Some of these patients (14 patients) were not included in the study because of the nature of their lesions. These tumors included five meningiomas, four cholesteatomas, two ependymomas, two arachnoidal cysts and one clivus chordoma. The remainder consisted of neuromas. Six of those patients with neuroma had to be excluded as well, because their lesions originated from other cranial nerves, specifically the hypoglossal nerve (n = 3), the trigeminal nerve (n = 2), and the facial nerve (n = 1). Three patients had to be excluded because they had bilateral ANs. One patient was excluded because he had Menière's disease contralaterally. Therefore, 206 unilateral ANs were seen in that period. Another 15 patients were excluded because their tumor was a recurrence after previous surgery in a different hospital. Twenty more cases were dropped because audiometric data had been obtained on those patients from referring institutions and were considered inadequate for detailed analysis because of possible lack of uniformity. This study thus pertains to the 171 remaining patients. Data on history, tumor size, pure-tone audiograms, and speech audiometry were analyzed. Each patient's history was taken from the chart. The subjective experience of hearing loss, tinnitus, vestibular symptoms, and other complaints was noted, and their duration was recorded. The size of the tumor was expressed as the maximum extrameatal diameter in the axial plane, parallel to the petrous ridge, as depicted by magnetic resonance imaging (before 1989, by computerized tomography). Whenever the tumor was confined to the internal auditory canal, the maximum diameter was taken. Pure-tone audiometry was performed at octave frequencies from 125 Hz up to 8 kHz with a maximum intensity of 125-dB hearing loss. Speech audiometry measurements with Dutch consonant-vowel-consonant words were performed up to a maximum intensity of 125-dB SPL (11). The speech reception threshold was assessed,

as well as the maximum discrimination with its corresponding loudness. For data analysis tone audiometry thresholds at 0.5, 1, 2, and 4 kHz were considered. In pure-tone audiometry, when no threshold could be assessed at 125-dB hearing loss, the level was registered as 130-dB hearing loss. Pure-tone thresholds of the affected and contralateral side were compared to the international standard of normal-hearing thresholds (ISO 7029). For each frequency, we compared the patient's threshold with the normal value adjusted for age. Parameters from the patient's history and the tumor size were compared to hearing loss as measured by pure-tone and speech audiometry. Additionally, the slope of the audiogram was taken as a parameter of hearing. This slope was defined as the difference between the average threshold at 2 and 4 KHz and the average threshold at 0.5 and 1 KHz. Correlation coefficients with $p< 5\%$ were considered statistically significant. Other significance levels are mentioned explicitly.

## RESULTS

### Patients, symptoms, and tumor size

This study included 92 males with a mean age of 49.5 years (range, 21-88 years) and 79 females with a mean age of 54.9 years (range, 19-80 years). The age difference between men and women is significant at the 1 % level. The average size of the tumors is 22.4 mm (range, 4-50 mm), the median being 22.0 mm. In this series, hearing loss, tinnitus, and vertigo occurred in various combinations (Table 1). In total, 145 (85 %) of the 171 patients had subjective hearing loss; tinnitus was reported by 91 (53%) of the patients and vertigo by 39 (23%).Other symptoms, such as headache, fullness in the ear, numbness of the concha, and trigeminal neuropathy, were mentioned sporadically but did not seem to be important to the patient.

Table 1 . Grouping of the patients according to the first noticed symptom: duration of the symptom before consultation and the size of the tumor.

| First noticed symptom | Number of patients [%] | Duration of the symptom before consultation [months] | | Size of the tumor [mm] | |
|---|---|---|---|---|---|
| | | mean | SEM | mean | SEM |
| Hearing loss only | 34.7 | 76.3 | 100.9 | 24.7 | 11.5 |
| Tinnitus only | 7.1 | 132.0 | 203.6 | 20.9 | 7.25 |
| Vestibular symptoms only | 5.3 | 18.7 | 25.5 | 23.9 | 11.7 |
| Hearing loss and tinnitus | 35.3 | 44.0 | 53.3 | 19.2 | 8.92 |
| Hearing loss and vestibular symptoms | 7.1 | 18.8 | 19.9 | 30.3 | 10.2 |
| Tinnitus and vestibular symptoms | 2.9 | 69.4 | 97.5 | 12.8 | 2.86 |
| Hearing loss and tinnitus and vestibular symptoms | 7.7 | 67.2 | 73.8 | 23.5 | 10.5 |

## Audiometry and tumor size

There appeared to be no significant correlation between the size of the tumor and several other variables, namely the threshold in the pure-tone audiogram, the threshold differences with respect to the contralateral ear, the audiogram slope, the speech reception threshold, and the maximum discrimination and its corresponding loudness. Furthermore, we distinguished two groups, group 1 having a tumor $< 20$ mm, and group 2 having a tumor $> 20$ mm. The results from the t-tests did not show a significant difference between the two groups for any of the parameters. The results essentially were the same when 15 or 10 mm was taken as the cutoff point between the two groups. In Table 2, mean values of the audiometric parameters are presented for these two groups.

Table 2. Descriptive statistics of audiometric parameters for the two groups.

| | Mean group 1 | Mean group 2 | t-test significance | N group 1 | N group 2 | SEM group 1 | SEM group 2 |
|---|---|---|---|---|---|---|---|
| Threshold affected side .5 kHz [dB HL] | 52.9 | 55.9 | 0.625 | 91 | 80 | 37.1 | 43.4 |
| Threshold affected side 1 kHz [dB HL] | 62.4 | 62.9 | 0.928 | 91 | 80 | 36.4 | 43.6 |
| Threshold affected side 2 kHz [dB HL] | 70.4 | 71.0 | 0.917 | 91 | 80 | 35.0 | 42.2 |
| Threshold affected side 4 kHz [dB HL] | 76.9 | 75.9 | 0.865 | 91 | 80 | 34.6 | 41.9 |
| Discrimination affected side [%] | 60.4 | 53.6 | 0.278 | 91 | 79[1] | 38.6 | 43.3 |
| Slope affected side [dB SPL] | 32.0 | 28.8 | 0.590 | 91 | 80 | 37.4 | 41.5 |
| SRT affected side [dB SPL] | 35.1 | 30.5 | 0.304 | 67 | 53[2] | 68.5 | 79.0 |
| Threshold difference .5 kHz [dB HL] | 38.6 | 42.2 | 0.553 | 91 | 80 | 35.8 | 41.9 |
| Threshold difference 1 kHz [dB HL] | 46.3 | 48.7 | 0.703 | 91 | 80 | 36.7 | 43.0 |
| Threshold difference 2 kHz [dB HL] | 52.1 | 55.6 | 0.543 | 91 | 80 | 35.6 | 40.3 |
| Threshold difference 4 kHz [dB HL] | 48.5 | 50.8 | 0.668 | 91 | 80 | 33.1 | 36.8 |

HL, Hearing Level; SPL, Sound Pressure Level; SRT, Speech Reception Threshold;
Group 1: tumorsize <= 20 mm; Group 2: tumorsize > 20 mm.

[1] One patient could not perform speech audiometry because of a language handicap.

[2] A total of 51 patients did not reach the 50% score.

## Audiometry and history

There appeared to be significant correlations between the duration of hearing loss and the thresholds in the pure-tone audiogram. This was found for the affected side as well as for the difference between the affected and contralateral side. These correlations imply that the longer the hearing loss was present, the more serious was the hearing impairment. Additionally, for the affected side, we found a significant correlation between the duration of deafness and discrimination loss (Table 3). Only 119 patients scored 50% or higher on speech audiometry. For this subgroup, the correlation coefficient between the duration of symptoms and the speech reception threshold is not significant. No significant correlation could be shown between the audiometric data and the durations of tinnitus and vertigo.

## Audiometry of the contralateral side

A slight, but significant, correlation was found between the pure-tone thresholds at 2 and 4 kHz of the contralateral ear and the duration of the symptoms of hearing loss. Moreover, the intensity at which the maximum discrimination was perceived in the contralateral ear correlated significantly with the duration of hearing loss (Table 3). At each frequency, Figure 1 shows the percentage of patients with a pure-tone threshold exceeding the

Table 3. Correlation between the subjective duration of hearing loss and audiometric parameters of the affected and contralateral side.

| | Correlation coefficient | No. of patients | p value |
|---|---|---|---|
| Threshold affected side 0.5 kHz | 0.32 | 171 | <0.001 |
| Threshold affected side 1 kHz | 0.33 | 171 | <0.001 |
| Threshold affected side 2 kHz | 0.38 | 171 | <0.001 |
| Threshold affected side 4 kHz | 0.35 | 171 | <0.001 |
| Mean threshold affected side 0.5, 1, and 2 kHz | 0.32 | 171 | <0.001 |
| Mean threshold affected side 1, 2, and 4 kHz | 0.32 | 171 | <0.001 |
| Discrimination loss affected side | 0.25 | 170[1] | 0.001 |
| SRT affected side | 0.11 | 120[2] | 0.224 |
| Threshold difference 0.5 kHz | 0.31 | 171 | <0.001 |
| Threshold difference 1 kHz | 0.29 | 171 | <0.001 |
| Threshold difference 2 kHz | 0.31 | 171 | <0.001 |
| Threshold difference 4 kHz | 0.24 | 171 | 0.002 |
| Threshold contralateral side 2 kHz | 0.18 | 171 | 0.021 |
| Threshold contralateral side 4 kHz | 0.23 | 171 | 0.002 |
| Intensity of maximal discrimination contralateral side | 0.16 | 170[1] | 0.037 |

SRT, speech reception threshold.

[1] One patient could not perform speech audiometry because of a language handicap.

[2] A total of 51 patients did not reach the 50% score.

90th percentile value of the normal-hearing population of the same age. The percentage is given for the affected side (Fig. 1A) and for the contralateral side (Fig. 1B). Our group of patients with AN have significantly worse hearing than the normal-hearing population on both the affected and contralateral side.

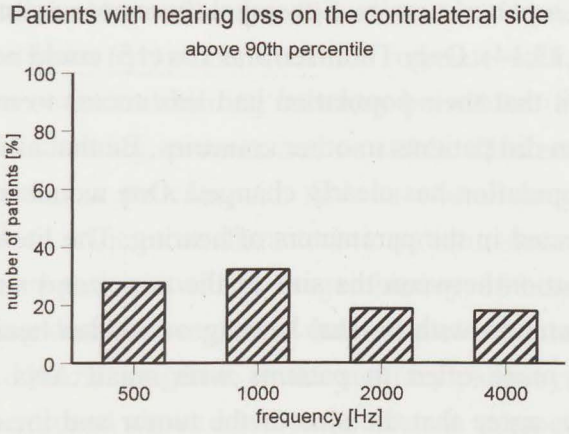


Figure 1A The percentage of patients with pure-tone audiometry at 0.5, 1, 2, and 4 kHz on the affected side exceeding the 90 percentile of the normal hearing population.

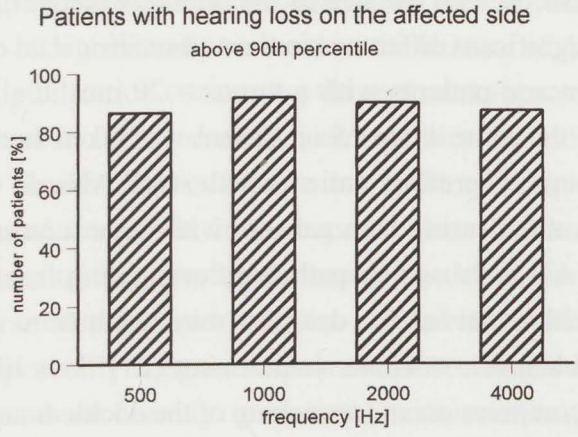


Figure 1B The percentage of patients with pure-tone audiometry thresholds at 0.5, 1, 2, and 4 kHz on the contralateral side exceeding the 90 percentile of the normal hearing population.

## DISCUSSION

More ANs have been identified in recent times because of the availability of modern imaging techniques. It has become easy to detect small tumors. Even asymptomatic ANs have been identified, sometimes just by chance (2,12). There is strong evidence that these techniques have led to a shift of the size range of reported tumors. Several authors note a decrease in tumor size over time (6,13,14). Only Thomsen and Tos (15) could not confirm this, but they do admit that their population had less access to magnetic resonance imaging than did patients in other countries. Be that as it may, the profile of the AN population has clearly changed. One wonders whether these changes are reflected in the parameters of hearing. The literature mentions some type of relation between the size of the tumor and audiometric data (16,17). A presentation with normal hearing or sudden hearing loss is reported to occur more often in patients with small ANs (18-20). Most authors, however, agree that the size of the tumor and the severity of the hearing loss are not correlated. That standpoint is confirmed for the group of patients in this study. The threshold profile in the pure-tone audiogram, the audiogram slope and the parameters of speech recognition showed no significant correlation with the size of the tumor. Moreover, Table 2 shows that there is no significant difference in the audiometric data of patients with a tumor< 20 mm and patients with a tumor > 20 mm in size. The results essentially were the same when 15 or 10 mm was taken as the cutoff point between the groups. Therefore, patients with small ANs do not necessarily have better or worse hearing than patients with large tumors. Hearing loss in patients with AN is caused by pathology originating from structures adjacent to the cochlear nerve. The deafness may result from cochlear, retrocochlear or cochlear-retrocochlear impairment (21). It is likely that some combination of compression and stretching of the cochlear nerve is involved in the pathogenesis of the sensorineural hearing loss (22,23). Moreover, changes in the vascular supply of the cochlea, biochemical alterations in the

inner ear fluids, hair cell degeneration, and dysfunction of the stria vascularis may play a role (24,25). This study suggests that the impact of each of these pathogenetic factors may vary in a way that does not depend on the size of the tumor.

The current investigation indicates that when the duration of the hearing loss is longer, the deafness is more severe, as expressed in a variety of parameters of pure-tone and speech audiometry. However, duration of tinnitus and vestibular symptoms does not correlate with the audiometric data. In ANs, sensorineural hearing loss may be sudden (even followed by improvement), fluctuating, progressive, or stable. This study supports the current opinion that in patients with AN, an overall progressive sensorineural hearing loss is the most characteristic pattern, since the hearing loss is more severe in patients with a longer history of hearing complaints. However, hearing disorders represent only part of the array of symptoms. The pathology does not originate in the auditory pathways. Therefore, the observations mentioned above have to be seen in perspective; the audiometric data reflect just part of the biologic process. Because hearing loss is not related to the size of the tumor (vide supra), the tendency for hearing loss to be progressive relates to all tumors, regardless of their dimensions.

In this group of patients, the hearing in the ear contralateral to the AN appeared to be significantly worse than the hearing of the normal population. The first publication concerning the contralateral ear in patients with an AN, published in 1977, showed abnormalities in auditory brainstem responses (26). Several studies concerning auditory brain stem responses have been reported since then. It has become clear that there is no consistency in the nature of the waveform abnormality. Moreover, there are indications that these abnormalities may be reversible after resection of the tumors (27). It generally is agreed that waveform changes in the contralateral ear are found exclusively in patients with relatively large tumors, although no relation was found between the type of these changes and the size of the tumor (28). The current study is the first to describe significant-

ly higher threshold levels for pure-tone audiometry on the contralateral side. This might be caused by a systemic error in the audiometry. Yet, that explanation is extremely unlikely, since the measurements are carried out over a period of 10 years by different persons who are fully qualified. In addition, the equipment used for these measurements is up to the highest technical standards. Alternatively, the discrepancy might arise because we compared hearing thresholds of the contralateral ear of the patients with an AN with the normal thresholds obtained from screened populations of otologically normal persons. However, anamnestically, there is no evidence that sensorineural hearing loss of any other origin in these patients would occur more frequently than in the normal population. Patients with known contralateral hearing loss (e.g., due to Menière's disease) were excluded. Brainstem compression by large tumors could contribute to the hearing loss on the contralateral side. In these cases, the auditory neural pathways are impaired, as shown by auditory brainstem responses (vide supra). However, this theory is not valid either, since the hearing loss on the contralateral side is distributed equally over the whole group of patients and is not restricted to patients with large lesions. An acceptable explanation is that the patients in this group have selected themselves beforehand. Unilateral slowly progressive hearing loss is likely to result in some type of habituation: the patient is able to cope with this impairment in everyday life. However, when the contralateral ear does is not function optimally either, it is more likely that the will seek medical advice. As a consequence, the diagnosis of an AN probably will be established more often in patients with a concomitant hearing loss in the contralateral ear. Tumors might remain undiagnosed when the patient has perfect hearing on the contralateral side. Eventually, the patients concerned may die of unrelated disorders, since ANs tend to grow slowly or be stable tumors (29, 30).

The significant difference in age between men and women with unilateral ANs may not have any importance. It is generally assumed that ANs remain dormant for a certain length of time. Then, at some point, symptoms

arise. Women tend to live longer than men; therefore, there is more time for an AN to become manifest in women. Moreover, the hearing in men is worse than in women at a given age (ISO 7029). This could be responsible for the phenomenon that men show up for consultation at a younger age than women. As a consequence, ANs may tend to be diagnosed at an earlier age and more frequently in men. On the basis of postmortem studies, the estimated incidence of ANs is nearly a thousand times more than the incidence that has been established in the general population (31). Our assumption that a certain category of ANs will remain undiagnosed may partly explain the enormous difference between the actual and the calculated incidence of the disorder.

The importance of hearing preservation after surgical removal of the tumor usually is played down by the advocates of the translabyrinthine approach (32). The results of this study provide arguments in favor of therapeutic strategies that seek to preserve hearing. The auditory handicap for the patient is not necessarily the result of the tumor-induced hearing loss alone. When hearing preservation is optimal and consistent, it will substantially contribute to a reduction of the postoperative (or postradiosurgical) morbidity in a relatively large proportion of patients.

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# 3

# CHAPTER 3

## ELECTRONYSTAGMOGRAPHIC CHANGES IN PATIENTS WITH UNILATERAL VESTIBULAR SCHWANNOMAS IN RELATION TO TUMOR PROGRESSION AND CENTRAL COMPENSATION

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## ABSTRACT

Vestibular function was studied in a group of 121 patients with unilateral vestibular schwannomas who were referred to University Hospital Utrecht, between 1986 and 1996. Testing included the caloric test, torsion test, saccade test, smooth pursuit test and the registration of spontaneous nystagmus. Each patient's symptoms were taken from a chart review. The size of the tumor was expressed as the maximum extrameatal diameter in the axial plane parallel to the petrous ridge as seen in magnetic resonance imaging or computerized tomography. Large tumors were significantly more often accompanied by a more severe paresis on caloric testing, a smaller gain on torsion testing, spontaneous nystagmus, an abnormal saccade test and an abnormal smooth pursuit test. The presence of spontaneous nystagmus was significantly more frequently combined with an abnormal smooth pursuit and saccade test. There was a significant correlation between the slow component's velocity of the spontaneous nystagmus and the size and progression of tumor. However, a specific relation between tumor size and central vestibular compensation could not be demonstrated.

## INTRODUCTION

The presence of a vestibular schwannoma (VS) may lead to vestibular symptoms that originate at different levels. Encasement of the vestibular nerves as a result of the stretching of axonsor compression of neuronal structures can possibly occur first and is a frequent finding. In larger tumors, compression of the brainstem and cerebellum may lead to disturbances of gait and equilibrium. Labyrinthine dysfunction can also be worsened by a tumor-induced compromised blood supply. Further intracranial extension of the tumor eventually blocks cerebrospinal fluid pathways. That blockage may also interfere with the process of relaying central as well as peripheral vestibular neuronal networks.

In the past, neurophysiological tests of the vestibular system were used as a filter to rule out or demonstrate the presence of a VS. With the advent of currently available imaging techniques, in particular magnetic resonance imaging, a VS can be detected with a higher sensitivity and specificity than was possible with neurophysiological tests of the vestibular system [5, 6, 9, 17-19, 21]. The objective of our study was to further our understanding of the growth and behavior of VS, particularly in those cases where follow-up and serial imaging are not performed preoperatively [3, 13].

Growth of a tumor can possibly lead to a unilateral lesion in the vestibular system. Such a lesion is usually permanent, but the consequent nystagmus and vertigo gradually abate after some time. This recovery is the result of a compensation mechanism operating in the central nervous system that rebalances persistent vestibular asymmetries [12, 16]. In a study by O'Leary et al. [15], a relation was shown between tumor size and eye asymmetry in an autorotation test as a result of a unilateral vestibular lesion.

The directional preponderance ascertained from caloric (DPC) and torsion testing (DPT) is a measure of the degree of compensation after unilateral labyrinthine hypofunction. It is known that tumor growth initiates labyrinth hypofunction with subsequent compensation mechanisms.

Therefore, we investigated the relation between tumor size, tumor progression and directional preponderance in patients with a unilateral VS. We also investigated other vestibular measures in the same patients.

## PATIENTS AND METHODS

In all, 121 patients with surgically and radiologically confirmed unilateral VS were referred to University Hospital, Utrecht, between 1986 and 1996. All patients were excluded who had undergone their diagnostic work-up in a referring hospital because vestibular measures might not have been recorded uniformly.

Vestibular examinations were performed by means of electronystagmographic registration. The analysis of nystagmus focused on the slow component's velocity (SCV). The direction of the nystagmus was identified as the direction of the fast component of the nystagmus. Procedures and normal values in this study were in accordance with internationally accepted guidelines adopted in 1992 [20]. The composite signal of the left and the right eye was analyzed. In addition to recording spontaneous nystagmus, vestibular tests included the caloric test, torsion test, saccade test and smooth pursuit test.

In the caloric test each ear was irrigated with water at 30°C and 44°C for 20 s at a rate of 200 ml/min. The response of each labyrinth was calculated. The difference between the two labyrinths and directional preponderance was also determined. Here DPC represented directional preponderance in the caloric test. Hypofunction of a labyrinth was found to be present when the SCV of the nystagmus after caloric stimulation with warm and cold water was $< 10^{\circ}$ per s. Unilateral vestibular paresis (also called "canal paresis") was recorded when the difference between the responses of the labyrinths was > 22%. DPC values > 23% were considered to be abnormal.

During the torsion test the patient sat in the dark on a chair that was sinusoidally rotated in a horizontal plane at a 120° amplitude. The gain and directional preponderance were calculated. Here DPT represented directional preponderance in the torsion test. The gain was defined as the quotient of the SCV of the nystagmus minus the velocity of the rotating chair. Normal values for the gain were between 25 and 90%. DPT was the difference between the SCV to the right and to the left, as expressed in percentages of the chair's velocity. DPT values > 20% were considered to be abnormal.

In the saccade test a visual stimulus appeared every 2 s and alternated 20° to the left and then to the right side of the patient. The smooth pursuit test involved moving a visual stimulus slowly and sinusoidally in the horizontal plane with a 40° amplitude; that is, it moved 20° to either side.

The size of each tumor was expressed as the maximum extrameatal diameter in the axial plane parallel to the petrous ridge, as depicted by magnetic resonance imaging or computed tomography. The maximum diameter was taken whenever the tumor was predominantly located in the internal auditory meatus. It was impossible to determine growth of a tumor retrospectively when no serial comparable imaging was available. Therefore, we estimated tumor progression by dividing the size of the tumor by the amount of time that had elapsed since the onset of first symptoms (i.e., hearing loss, tinnitus or vertigo) as recorded on the patient's chart.

For statistical analysis, a $P$ value < 5% was considered to be statistically significant.

## RESULTS

As shown in Fig. 1, the overall group of patients consisted of 66 men (mean age, 49.1 years) and 55 women (mean age, 54.4 years). The mean age of the group was 51.5 years. The difference in age between sexes was significant

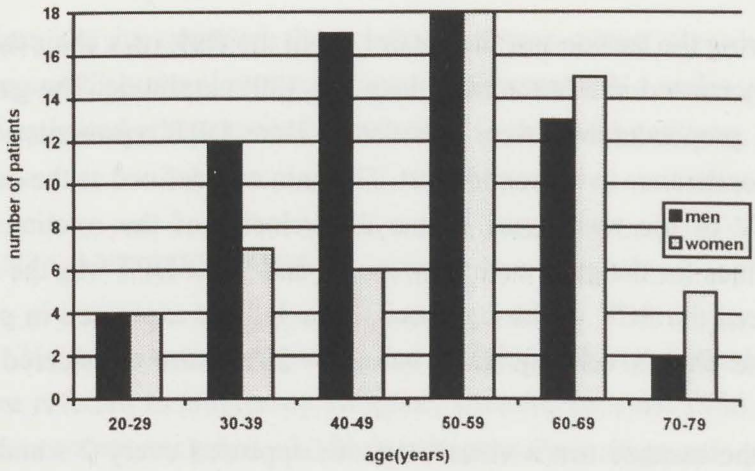


Fig. 1 Distribution of age for male and female patients with VS at University Hospital Utrecht.

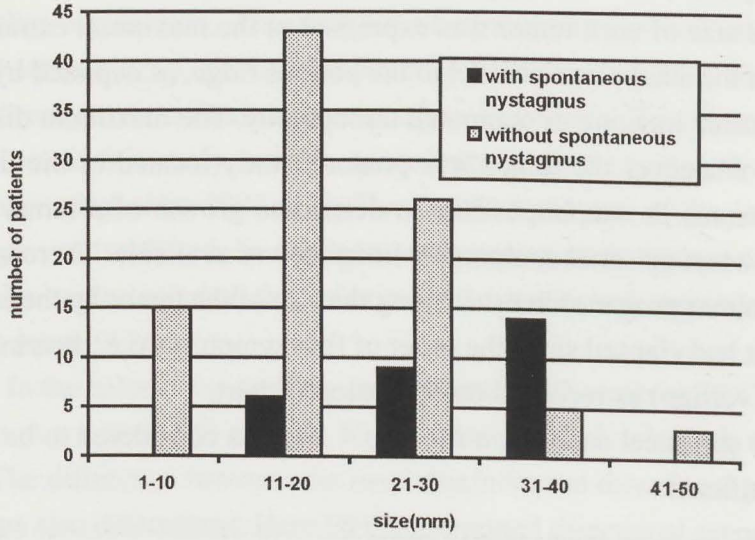


Fig. 2 Distribution of tumor size. Bars are split to distinguish between patients who did (solid) and did not (shaded) have spontaneous nystagmus.

(*t*-test; $P = 0.026$). There was no significant difference between male and female patients with regard to tumor size. The mean size of the tumor was 22.1 mm, ranging from 4 to 50 mm (Fig. 2).

Caloric testing was performed in 121 patients. Vestibular paresis was demonstrated in 96 cases. This paresis was complete (100%) on the affected side in 37 patients. An abnormal DPC was found in 48 patients, only 28 of whom had a DPC to the contralateral ear (Table 1). However, a significant correlation was found between tumor size and vestibular paresis ($r = 0.392$; $P < 0.001$). Thus, the larger the tumor, the greater the paresis (Fig. 3). Some correlation was also found between tumor progression and vestibular paresis ($r = 0.1955$; $P = 0.032$). In contrast, no significant correlation was found between tumor size and DPC or between tumor progression and DPC. Age was not significantly correlated with DPC.

The torsion test showed an abnormal DPT in 45 cases. However, no significant correlation could be demonstrated between the size or progression of tumor and DPT. No significant correlation was seen between

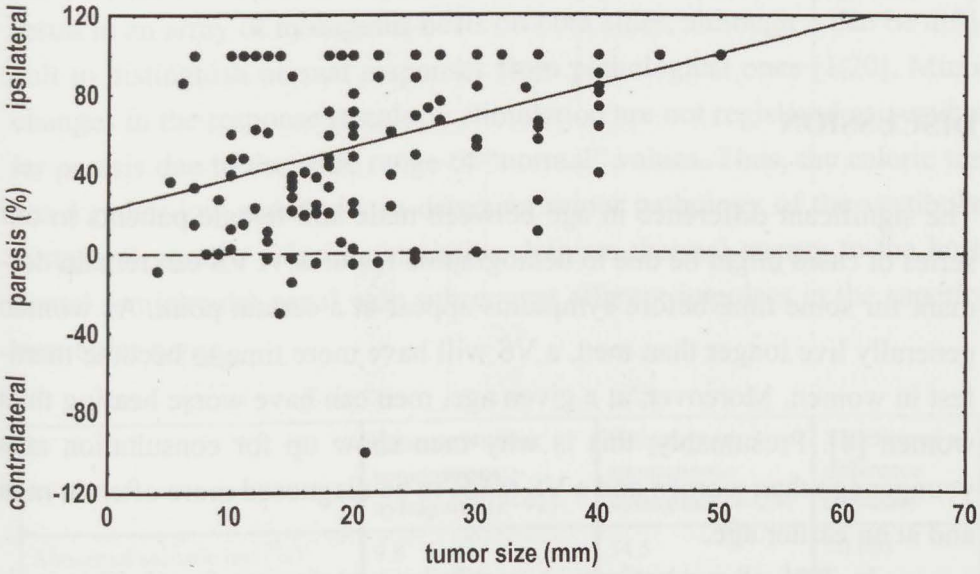


Fig. 3 Vestibular paresis as a function of tumor size. Ipsilateral paresis is denoted as a positive number, contralateral paresis as a negative number. Some data points overlap in this scatter plot. The line corresponds with the best linear fit.

DPT and age. A gain of less than 25% was found in 85 patients. A significant negative correlation was found between tumor size and gain ($r$ = -0.1883; $P$ = 0.039), and a smaller gain was found in larger tumors.

In 29 patients an abnormal smooth pursuit was seen. In 19 patients, the results of the saccade test were abnormal and 29 patients had a spontaneous nystagmus, varying from 1° to 15° per s (Table 1). Comparing the patients who showed a spontaneous nystagmus ($n$ = 29) with those who did not ($n$ = 92), a significant difference was noted in tumor size (Fig. 2; Table 2). Of the patients with a spontaneous nystagmus, 10 had an abnormal saccade test and 14 demonstrated abnormal smooth pursuit. For both tests, the number of patients with abnormal results was significantly higher than among VS patients who had no spontaneous nystagmus. The SCV of the spontaneous nystagmus correlated significantly with tumor progression ($r$ = 0.394; $P$ = 0.035; $n$ = 29) and tumor size ($r$ = 0.406; $P$ = 0.029; $n$ = 29).

## DISCUSSION

The significant difference in age between male and female patients in our series of cases might be due to demographic features. A VS can remain dormant for some time before symptoms appear at a certain point. As women generally live longer than men, a VS will have more time to become manifest in women. Moreover, at a given age, men can have worse hearing than women [8]. Presumably, this is why men show up for consultation at a younger age than women and a VS tends to be diagnosed more often in men and at an earlier age.

In 79% of our patients, a vestibular paresis was found. This incidence is in accordance with data from the existing literature [7,11]. Theoretically, a certain degree of hyporeflexia is to be expected in all VS patients. The nature of this disorder implies some type of blocking of axons of the vestibular nerves. There are two theories that could explain why

| | | Patients($n$) | Patients(%) |
|---|---|---|---|
| Caloric test | Partial vestibular paresis | 96 | 79.3 |
| | Complete vestibular paresis | 37 | 30.6 |
| | Abnormal DPC | 48 | 39.7 |
| Torsion test | Abnormal DPT | 45 | 37.2 |
| | Abnormal low gain | 85 | 70.2 |
| Spontaneous nystagmus | Present | 29 | 24.0 |
| Smooth pursuit test | Abnormal | 29 | 24.0 |
| Saccade test | Abnormal | 19 | 15.7 |

Table 1 Vestibular findings in 121 patients with unilateral VS.

vestibular paresis could not be demonstrated in all VS patients. First, there is a problem in the definition of vestibular paresis. Caloric stimulation may result in an array of nystagmus beats on both sides, although it can be difficult to distinguish normal responses from pathological ones [1,20]. Minor changes in the response to caloric stimulation are not registered as vestibular paresis due to the wide range of "normal" values. Thus, the caloric test has a rather low sensitivity in detecting minor pathology of the vestibular system. Secondly, caloric stimulation delivers thermal energy to the horizontal semicircular canal with subsequent afferent impulses in the superior vestibular nerve.

| | Patients without spontaneous nystagmus ($n$=92) | Patients with spontaneous nystagmus ($n$=29) | Significance of difference ($P$-value) |
|---|---|---|---|
| Abnormal saccade test (%) | 9.8 | 34.5 | <0.001 |
| Abnormal smooth pursuit(%) | 16.3 | 48.3 | <0.001 |
| Tumor size (mm) | 19.7 | 29.8 | <0.000001 |

Table 2 Percentage of patients with an abnormal saccade or smooth pursuit test compared to tumor size in patients with or without spontaneous nystagmus.

As a result of the effects of caloric stimulation it is presumed that vestibular paresis can only be expected in tumors arising from the superior vestibular nerve. Yet, even when a tumor does arise from that nerve, it is not always possible to demonstrate vestibular paresis. According to Okada et al. [14] this phenomenon is related to the size of a lesion. They postulate that larger tumors are more likely to block axons of the superior vestibular nerve than smaller ones. Although it was previously considered that a VS mostly originated in the superior vestibular nerve [19], there is strong evidence that tumors frequently come from the inferior vestibular nerve [4, 22]. Moreover, a tumor originating in the inferior vestibular nerve can lead to vestibular paresis as well, presumably by compression of the superior vestibular nerve. Admittedly, current understanding of the exact origin of a VS is incomplete and inconsistent. It is conceivable, however, that some tumors might be incapable of reducing afferent vestibular impulses.

Patients with a fast-growing or biologically active VS are expected to have vestibular complaints. The reason is that the blockage of axons and a consequent vestibular asymmetry cannot be accommodated fast enough by a central compensation mechanism. As long as the vestibular imbalance is not compensated, there will be a directional preponderance in the direction of the contralateral side. Two measures for the imbalance of the vestibular system are DPC and DPT.

In our study both DPC and DPT failed to correlate significantly with tumor progression. The reason for this might be that it is impossible to determine tumor growth retrospectively. This occurs because it is not known accurately at which point hearing loss, tinnitus or vestibular symptoms appear in the course of a VS. Tumor progression, as defined in this study, is merely an estimate of tumor growth. Additionally, the effectiveness of the compensation mechanism can be related to age. Presumably, compensation is a process of multiple mechanisms, in which unknown and imponderable features play a role. Prospective studies are needed to elucidate how the growth and biological activity of a tumor are related to directional prepon-

derances as obtained from vestibular tests.

In our present study, we could confirm the finding that the percentage of vestibular paresis is related to the size of a tumor [2, 7, 10]. Apparently, larger tumors are accompanied by a more pronounced hypofunction of the labyrinth. It is yet unclear whether this is the result of the blockage of afferent axonal pathways or a decreased excitability of the labyrinth itself. Our observations suggest that caloric testing is more sensitive in the detection of large tumors. Patients with large tumors also show a smaller gain in torsion testing. That is, activity is lost on the affected side and there is an ensuing reduction in afferent pathways of the vestibulo-ocular reflex. Thus, a high percentage of vestibular paresis shown by caloric testing in combination with a small gain shown by torsion testing indicates the presence of a large VS. This phenomenon seems to be a logical result of the anatomical relationships created by a bulky tumor in the cerebellopontine angle. Large lesions are more likely to lead to apraxia of vestibular nerves. At the same time, they are likely to put pressure on intracranial structures and compromise the labyrinthine blood supply.

A spontaneous nystagmus was observed in 24% of our patients; all of those so afflicted had relatively large tumors. The SCV of the spontaneous nystagmus correlated significantly with the size and progression of the tumor and might be indicative of the biological activity of the VS. The SCV of the spontaneous nystagmus was faster when the size of the tumor was larger and its progression more pronounced. Under both conditions, greater asymmetry of labyrinthine function might be expected. This asymmetry is supposed to be responsible for the SCV of the spontaneous nystagmus. Moreover, patients with spontaneous nystagmus had an abnormal smooth pursuit or saccade test significantly more often. These features are supposed to be caused by the impairment of vestibular pathways at a more central level. Local anatomical relationships that depend on the presence of a large tumor are undoubtedly responsible for these findings.

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# 4

# CHAPTER 4

## ASSESSMENT OF VESTIBULAR SCHWANNOMA GROWTH; APPLICATION OF A NEW MEASURING PROTOCOL TO THE RESULTS OF A LONGITUDINAL STUDY

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## ABSTRACT

This study pertains to a group of 44 patients with a unilateral vestibular schwannoma (VS) who did not undergo surgery. Prospectively, the dimensions of the tumor were depicted at regular intervals by way of MRI and then judged by an otorhinolaryngologist and a neuroradiologist independently. Retrospectively, the size of the tumor was quantified by measuring the maximum surface of the lesion in the axial plane. The retrospective surface measurements confirmed the assessments made in the prospective part of the study: growth in 18% and shrinkage in 7%, while 75% remained unchanged. This approach is a pragmatic means to determine whether the size of a tumor has changed in the course of time.

## INTRODUCTION

The rationale behind any vestibular schwannoma (VS) operation is that the tumor is presumed to be growing and thereby poses a threat to the patient by causing further deterioration. Besides hearing loss, it will eventually lead to serious and progressive neurologic deficits that may have a fatal outcome. The aim of this study is to contribute to current knowledge about the natural history of VSs by reporting on a longitudinal study that we conducted in patients with an VS who did not undergo surgery.

Magnetic resonance imaging (MRI) is generally considered the most accurate means to depict VSs. MRI can be used to establish the dimensions of a tumor in various ways. It seems practical to take the maximum surface of the lesion in the axial plane as a measure of tumor size. However, this method has not been validated. Therefore, a secondary aim of this study is to determine whether changes in the measured surfaces of a lesion correspond with changes in tumor size as judged by independent observers.

## MATERIAL AND METHODS

This longitudinal study pertains to a group of 44 patients with a unilateral VS who were referred to the University Hospital Utrecht between 1990 and 1997. The diagnosis of VS in these patients was based on highly characteristic histories, audiovestibular symptoms, and imaging features. The patients' status was followed, whereby the dimensions of the tumor were recorded prospectively at regular intervals on MRI. This procedure was carried out with T1-weighted pulse sequences. The TR was 500 ms, the TE 30 ms, the number of averages 4, and the slice thickness was 3.0 mm with a gap of 0.3 mm. Sagittal and coronal surveys were used to ensure a scan plane through both internal auditory canals. A transverse scan was made. No angulation was used for this scan. In some patients this could have resulted

| *Age* | *<50 years* | *50-59* | *60-69* | *>70* |
|---|---|---|---|---|
| *decision of the patient* | 11 | 6 | 1 | 1 |
| *refusal despite advice for surgery* | - | - | 2 | - |
| *age* | - | - | 10 | 8 |
| *physical condition* | - | - | 1 | 3 |
| *tumor in better-hearing ear* | - | - | 1 | |

Table 1. The number of patients who did not have therapy, tabulated according to their age and rationale for conservative management.

in slightly different scan planes in relation to the tumor. However, a difference of a few degrees is unlikely to result in significant differences in tumor size. The reasons why these patients were not treated are listed in Table 1. We included only those patients who had been followed for at least 1 year and of whom at least 2 scans had been taken. Two observers (an otorhinolaryngologist and a neuroradiologist) made an independent visual assessment of each MRI print to detect possible changes in tumor size.

The retrospective part of this study consisted of recording the size of the tumor in consecutive scans for each patient. To quantify size, the maximum surface of the lesion depicted in the axial plane was measured. This maximum surface was used as a measure of tumor size. Only one picture was used from each MRI session. The one that represented the maximum size was taken. The picture to be used for the measurement was chosen on the basis of visual inspection. In case of doubt, the picture with the largest lesion surface was selected. The measurement was performed with an IBAS/VIDAS image analysis system (Kontron/Zeiss, Eiching). Each of the selected pictures was placed on a light box and scanned with a camera (Sony b/w CCD, type XC-77CE, Tokyo) mounted on a macroscope stand. For each print, the image analysis system was calibrated by aligning the ruler that was included on the picture. The images were subsequently digitized and

enhanced (frame size 768 x 512 pixels; 256 gray levels). The edges of the tumor were manually traced and the surface was then measured (Fig 1). Each measurement was performed by two observers independently. The average of the two observations was taken as the size of the tumor.

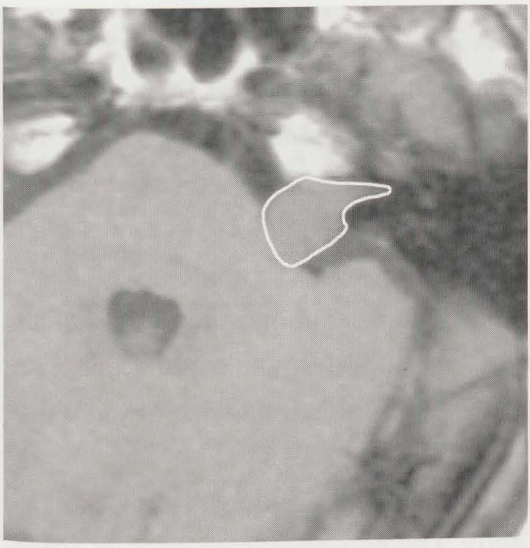

Fig. 1 The measurements could be performed after manually tracing the boundaries of the maximum surface of the tumor in the axial plane.

For each patient at each test moment, one value for the size of the tumor was obtained by averaging the measuring results of the two observers. The measurements were repeated during a follow-up period. In this way, we obtained a series of tumor sizes for each patient. Per patient, we then calculated the mean and the standard deviation (SD) of the tumor size. Since the length of the follow-up period was different in many patients, the number of measurements of tumor size that were available varied between 2 and 7 per patient (average 3.7 measurement per patient). The SD was taken as an indicator of growth or shrinkage of the tumor. In other words, the SD will be rather large for a tumor that is either growing or shrinking. A parameter of growth (PG) that equaled the SD was introduced. The parameter was given a negative sign if the tumor was shrinking. Thus, shrinkage could be determined from the consecutive tumor surfaces of the individual subjects. If the tumor hardly changed in size over time, the SD can be interpreted as the reproducibility of the measurements. We introduced an overall threshold (THR) for PG, whereby patients' lesions with a PG value above the upper threshold (+THR) can be considered growing tumors. Patients whose lesions got a PG

value below the lower threshold (-THR) were said to have a shrinking tumor. THR was defined as the average value of one SD of all patients.

## RESULTS

Twenty-nine male and 15 female patients entered the study. Their mean age was 58 years (range 29-76) at the time of the first MRI. The prints of 164 scans were examined. Per patient, an average of 3.7 MRIs were taken (range 2-7). The mean follow-up period was 3.5 years (range 12-74 months). The time between 2 subsequent scans ranged from 6 to 20 months, with a median of 12 months. There were no discrepancies among judgments of the two observers in the prospective part of this study. Growth could be assessed in 8 patients (18%) and shrinkage in 3 (7%), whereas the size of the tumor remained unchanged in 33 patients (75%).

In the retrospective part of this study, the judgments of the two observers appeared to vary only slightly. The pair-wise interobserver agreement was excellent, since the coefficient of correlation between the values they obtained was 0.9978 ($P<0.0001$, Fig 2). In Fig 2, the individual patients are represented by their patient number on the x axis and their PG value on the y axis. THR was calculated as described above and equals 18.2. This value is represented by the horizontal lines at 18.2 and -18.2. The results of the measurements were in accordance with the findings of the otorhinolaryngologist and the neuroradiologist who had visually interpreted the MRIs. The 8 patients with a PG value above THR were the same ones identified by these observers as having a growing tumor. Similarly, both procedures - visual inspection and measurement of the lesion on the MRI print - identified the same 3 patients with a shrinking tumor.

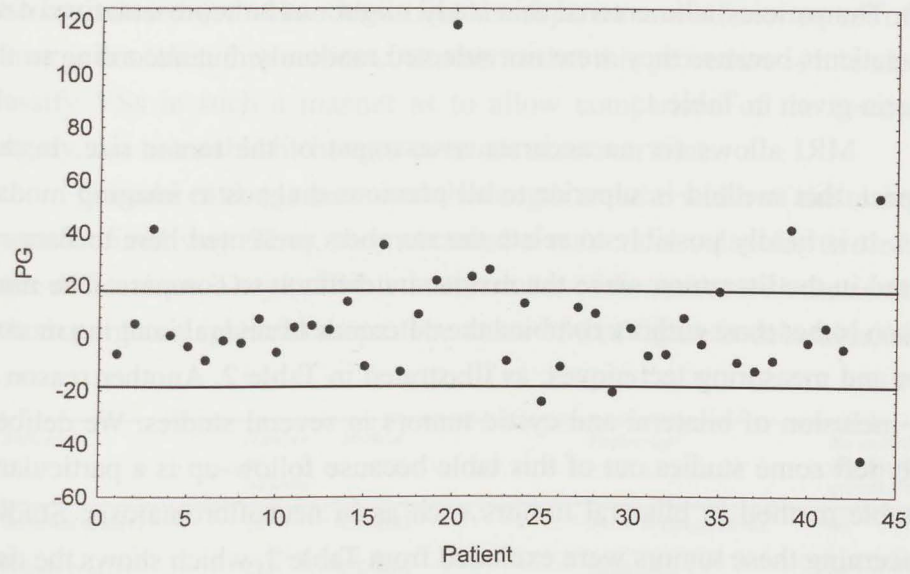


Fig. 2 Results of consecutive measurements. A parameter of growth (PG [mm2]) above the upper threshold or below the lower threshold (horizontal lines) represents respectively growth or shrinkage. When the PG lies between these thresholds the tumor size is considered to be unchanged.

## DISCUSSION

The body of literature on surgical series and operative techniques is extensive. In contrast, few studies have been done on the natural history and growth characteristics of VSs. And most of those studies refer to laboratory investigations on histologic specimens obtained at surgery. In that light, any conclusions that have been drawn on the progression of VSs must be based on some degree of conjecture. The problem is that growth of these tumors is determined by various factors that are poorly understood. The only way to obtain definite data on the clinical behavior of VSs is to follow the patients and record relevant clinical parameters at regular intervals. In particular, the dimensions of the tumor must be noted. However, ethical considerations always impair the composition of a group of patients to be included in a randomized longitudinal study. The present study is no excep-

tion. The patients who entered this study might not be representative of all VS patients because they were not selected randomly, but according to the criteria given in Table 1.

MRI allows for an accurate assessment of the tumor size. In this respect, that method is superior to all previous diagnostic imaging modalities. It is hardly possible to relate the numbers presented here to data reported in the literature, since the results are difficult to compare. The main reason is that most authors combine the outcomes of several imaging modalities and measuring techniques, as illustrated in Table 2. Another reason is the inclusion of bilateral and cystic tumors in several studies. We deliberately left some studies out of this table because follow-up is a particularly suitable method in bilateral tumors such as in neurofibromatosis. Studies concerning these tumors were excluded from Table 2, which shows the data summarized from the literature. Out of the 14 series in the literature, as shown in this table, the measurements were restricted to just one imaging modality in only 5 series. Unlike most studies in the series from the literature, only one imaging modality was applied in the present study. Furthermore, a new protocol was used to assess the size of the tumor and any possible changes between consecutive observations.

Studies in the literature express tumor size in diverse ways. The most common procedure is to measure the maximum diameter of the tumor (1,2). However, this entails gross simplification, since tumors are three-dimensional structures. Moreover, a change in the diameter implies an exponential change in the volume of the lesion. For example, when the diameter has doubled, the volume has increased eight times, assuming that the shape of the tumor has not changed. Thus, it is not sufficient to express growth in terms of diameter alone. To overcome this problem, various solutions have been worked out.

The American Academy of Otolaryngology-Head and Neck Surgery recommends estimating the tumor size by taking the square root of the product of the two standardized diameters in the axial plane (3). This procedure

also has some drawbacks. One is that the superior and inferior extent of the tumor is not taken into account. Another is that this procedure is intended to classify VSs in such a manner as to allow comparison of the results of surgery, not to establish changes in tumor size over time.

Charabi et al. (4) measured the length and the width of the tumor in a standardized way. Thus, they obtained a numerical value for two of the three dimensions. They calculated the volume of the tumor with the assumption that it has a spheroid shape. The value of that figure is debatable, since

| *Authors* | *Number of patients* | *Method* | *Follow-up*[2] | *No growth or negative growth (%)* |
|---|---|---|---|---|
| Bederson et al.(12) | 70 | CT/MRI | 24-28 m (mean 26 m) | 46 |
| Charabi et al.(4) | 123 | CT/MRI | mean 3.4 y | 26 |
| Deen et al.(13) | 68 | MRI | mean 3.4 y | 71 |
| Glasscock et al.(14) | 34 | MRI | 5-108 m (mean 28.5 m) | 44 |
| Laasonen & Troupp (15) | 21 | CT | 6 m-4 y | 33 |
| Levo et al.(16) | 24 | MRI | 1-6 y (mean 2 y) | 58 |
| Martin et al.(17) | 39 | MRI | 6 m-14 y | 67 |
| Nedzelski et al.(18) | 50 | CT/airCT/MRI | 7-152 m | 52 |
| Sarazin et al.(6) | 15 | MRIvolumetry | mean 428 d | 73 |
| Silverstein (19) | 11 | CT/MRI | 15-108 m | 73 |
| Strasnick et al.(20) | 51 | CT/ MRI | 6 m-11 y (mean 2.6 y) | 78 |
| Thomsen & Tos (21) | 21 | CT/airCT/poly-tomography | 1-16 y (mean 4.2 y) | 86 |
| Valvassori & Guzman (22) | 35 | CT/MRI/cisternogram | 8 m-12 y | 43 |
| Wiet et al.(23) | 53 | CT/ MRI | mean 2.13 y | 60 |
| Present series | 44 | MRI | 12-72 m (mean 3.5 m) | 82 |

Table 2. Series in the literature with conservative management of vestibular schwannomas[1]; the number of patients included, the imaging modality, the follow-up period, and the percentage of tumors that showed no growth or negative growth.

[1] Series with less than 10 patients are not mentioned

[2] d=days, m=months, y=years

VSs also may take the shape of a globe, pear, dumb-bell, cigar etc. or even be irregularly lobulated (5). Moreover, the volume of the intracanalicular part of the tumor is not measured. Only an estimated intracanalicular tumor volume is added to the calculated extrameatal part of the tumor. This may lead to inaccuracies when one tries to determine changes in tumor volume in time. As stated above, many authors describe growth in terms of an increase in diameter. By using the method of Charabi et al., the numerical indicators of growth increase up to the third power since the formula that is used yields the product of the three dimensions of the tumor. As a consequence, growth is presented in numbers that are substantially higher than found with other procedures.

The method described here also has some drawbacks. However, all (potential) errors are presumed to be randomly distributed through the series of measurements. The assessment of changes in tumor size pertains to a series of observations. Minor variations are considered to be an intrinsic part of the method used here. Therefore, only those changes that exceed a certain limit (vide supra) are considered to be meaningful and true representation of reality.

Computer-assisted volume calculations, derived from MR images, seem to be the best solution to the problem (6). Theoretically, volumetric MR measurements would be optimal, if consecutive slices with a maximum thickness of 1 mm were used. With thin slices, the tumor would be depicted on multiple slices. Moreover, the influence of partial volume effects would be marginal. A slice orientation in the sagittal plane would, in the majority of tumors, provide the most slices and lead to the most accurate volume calculation. Also, a volumetric method with thin slices would minimize the influence of different scan angles. Nevertheless, we used 3 mm-slices with a 0.3-mm slice gap. The main reason is that this pulse sequence had been used from the start of the study in 1990. It was eventually applied in all patient visits, because it remained available on new MR equipment at our hospital. The slices that can be obtained with this pulse sequence are of

limited value for a volumetric measurement. That is especially true for small VSs, because the tumor will be covered by only a few slices. In this study, the possible changes in tumor size as depicted on MRI were initially visually judged by a neuroradiologist and an otorhinolaryngologist. Obviously, their judgments were based on a subjective, visual estimation of tumor size as seen on the consecutive MR images. The method described here was used in an attempt to objectify their judgment. It entailed outlining the maximum surface of the tumor on an axial slice. This surface was considered to be a parameter of the size of a tumor. The method enabled us to overcome problems that would have arisen if volumetric measurements were used with the pulse sequence as described above. Only the image that showed the maximum size of the lesion was used. The surface measurement appears to be a practical solution to some problems in the assessment of changes in tumor size. It enables us to determine changes in tumor size on MR images that are obtained through the years with different generations of MRI scanners. As mentioned above, all methods described in the literature have their specific disadvantages and may result in erroneous outcomes. An important conclusion of this study is that the method we used has proven to be as reliable as the judgments of MR images by clinicians. This indicates that the figures presented in this study with respect to changes in tumor size are realistic. In future studies, volumetric assessments will certainly be possible with the new sophisticated imaging techniques that are available today. The value of the threshold THR, being the average of the individual SD values, can be considered as rather arbitrary and needs validation.

The observations presented here give rise to several considerations. Sometimes, in surgery for VSs, minor tumor fragments are left behind deliberately, mainly in order to preserve the continuity of the facial nerve. This is caused by the fact that there is no plane of cleavage between the facial nerve and the tumor (7,8). It has been demonstrated that this is also likely to occur when hearing conservation is pursued, since the interface between the tumor and the axonsof the cochlear nerve is neither sharply

delineated (9,10,11). Nevertheless, recurrences are very rare in these cases. It is conceivable that the natural behavior of VSs is responsible for this lack of demonstrable recurrences after surgical procedures that are obviously not radical. An explanation may be that the tumors have reached a (meta)stable phase. Then the doubling time of the remaining small amount of tumor cells is so long that it is impossible to demonstrate apparent regrowth of a tumor during a patient's lifetime. The result of stereotactic radiosurgery should also be considered in the light of the natural course of the disorder. In view of the observations mentioned above, it does not seem impossible that, after radiosurgery, failures might occur in patients in whom pronounced growth of the tumor is an intrinsic part of the disease, while radiosurgical success might occur in at least part of the tumors that are not growing.

Finally our results suggest once again that "watchful waiting" is a realistic and justifiable alternative to treatment, particularly in patients who have small vestibular schwannomas. Follow-up with repeated MRI studies remains mandatory in these cases. Treatment may then be postponed until growth has been definitely established.

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# 5

# CHAPTER 5

## VESTIBULAR SCHWANNOMA: PREDOMINANCE OF ANTONI TYPE B CELLS IN TUMORS OF PATIENTS WITH VESTIBULAR PARESIS

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## ABSTRACT

**Objective:** This study aimed to investigate whether in patients with a vestibular schwannoma (VS) the presence or absence of vestibular symptoms is related to histological characteristics of the tumor.

**Study design:** The study design was a retrospective clinical study.

**Setting:** The study was conducted at a tertiary referral center.

**Patients:** A group of eight patients with a unilateral VS and a normal vestibular function was compared to a group of VS patients, matched for tumor size, with vestibular paresis.

**Methods:** In this study the methods comprised vestibular examination of the patients and morphometric analysis of the histological specimens of their tumors.

**Main outcome measures:** The outcomes were measured by vestibular function and by the relative quantity of Antoni type A or type B cell tissue.

**Results:** The tumors of patients with vestibular paresis appeared to contain significantly more Antoni B cells and fewer Antoni A cells compared to the tumors of patients with a normal vestibular function.

**Conclusions:** Besides morphologic differences, type B cells may display a distinct behavior compared to type A cells. Presumably, in VS patients the development of a vestibular paresis appears to be related to the biological activity of type B cells in the tumor.

## INTRODUCTION

Vestibular symptoms are frequently registered in patients with a vestibular schwannoma(VS). In the literature, significant correlations have been demonstrated between the size of the tumor and several parameters of vestibular functioning. Abnormalities in the vestibular physiology tend to be more predominant in patients with large tumors. However, normal as well as abnormal test results may be encountered in patients with a VS of the same size. In VS patients, the size of tumor is apparently not the only determining factor in the pathophysiology of the labyrinth or its afferent pathways. Certain histological features of the tumor might also play a role. The aim of this study was to investigate whether equally sized tumors showed histological differences that were related to the presence or absence of vestibular symptoms.

## PATIENTS AND METHODS

Between 1986 and 1997, 191 patients with a unilateral VS were seen in the Department of Otorhinolaryngology of the University Hospital Utrecht. A thorough vestibular examination was performed in 121 of these patients and the data was uniformly recorded. The cases that were included in this study were selected from these 121 patients.

Vestibular examinations were performed by means of electronystagmographic registration. In each patient the examination included recording of spontaneous nystagmus, a caloric test, torsion test, saccade test, and a smooth pursuit test. For the purposes of this study, the analysis was restricted to the results of the caloric test. During this examination each ear was irrigated with water at 30° and 44° C for 20 s at a rate of 200 ml/min. The response of each labyrinth was registered. In each patient the difference between the labyrinths and the directional preponderance were calculated.

The labyrinth was found to function normally when three conditions were met during bithermal caloric testing: 1. the slow component's velocity of the nystagmus after stimulation with warm and cold water was > 10° per s; 2. the absence of vestibular paresis could be demonstrated through the fact that the difference between the responses of the labyrinths was < 22%; and 3. the directional preponderance was < 23%. The procedures and baseline values that were used in this study comply with internationally accepted guidelines (1). According to these criteria, eight patients had a normal vestibular function and could thus be included in this study. Each of these patients was matched for tumor size with a VS patient who had vestibular hypofunction, defined as a condition in which the results of the vestibular examination with bithermal caloric testing did not meet all three criteria stated above. All patients in the latter group had a severe vestibular hypofunction: the mean slow component's velocity of the nystagmus was 1.5% per s (range 0-8) and the mean difference between the responses of the labyrinths was 82% (range 25-100%). A pair was considered a good match if the difference in tumor size was less than 10%. The tumor size was expressed as the maximum extrameatal diameter in the axial plane, parallel to the petrous ridge, as depicted by magnetic resonance imaging or by computerized tomography. The images of all patients included in this study were closely examined to assess the extension of the tumor into the internal auditory canal. This was done in order to detect any medial tumors, which are likely to be asymptomatic (2). In all 16 patients included in this study, the diagnosis of vestibular schwannoma was histologically confirmed postoperatively.

Specimens from the tumors of these 16 patients were processed routinely to paraffin wax. Slides were subsequently stained with hematoxylin and eosin. Black-and-white photos were taken of the slices. Then areas containing Antoni A cells, Antoni B cells, and degeneration were identified on the photos under 200x magnification (Zeiss, Oberkochen, Germany). Type A cell tissue has a compact structure consisting of merging and diverging streams of elongated spindle cells. The nuclei tend to be aligned in straight

or curved rows, resulting in a palisade pattern. Type B cell tissue is characterized by a loose texture and polymorphism of the tumor cells. In this study, each of these three areas on the image was manually shaded with a different color (Figure1). For each patient, the presence or absence of iron was documented as well. The surface of the areas was measured using a computer-assisted plotting device (Zeiss Videoplan, Oberkochen, Germany). Subsequently the size of each area was expressed as a percentage of the total transectioned surface. During the histological examinations the patients' status was not known to the investigator. The statistical analysis consisted of comparison of the histological parameters in the two groups. A two-sided paired *t* test was used for this purpose and the results were adjusted for age differences.

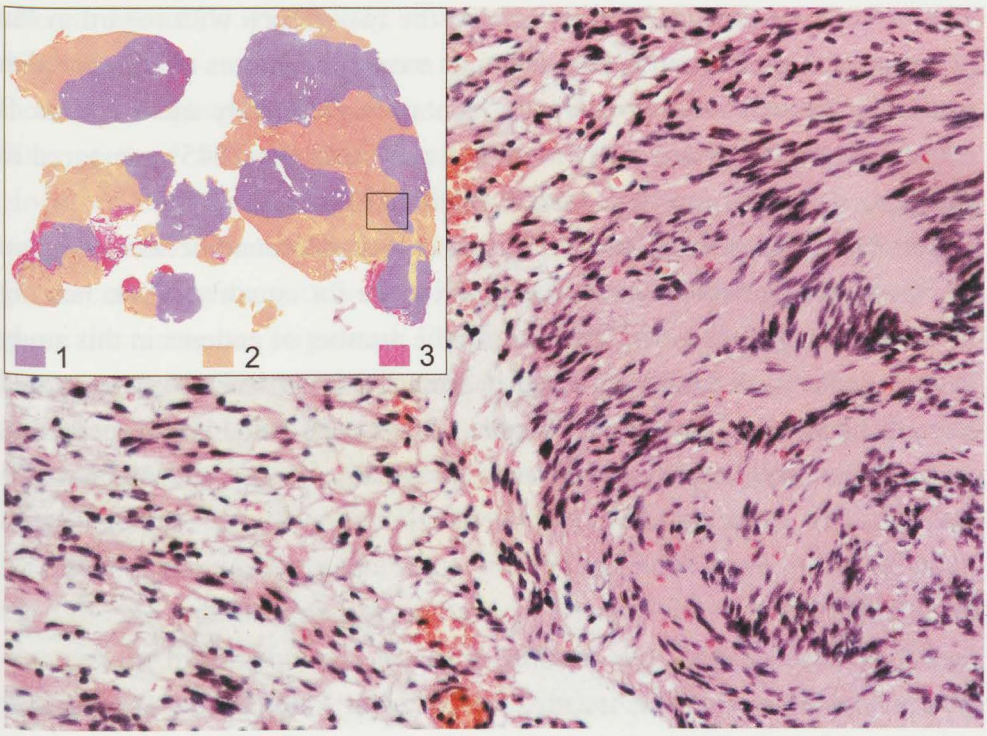


Fig. 1 Areas containing Antoni A cells(1), Antoni B cells(2), or degeneration(3) were identified and manually shaded with different colors, after which the surface of the areas was measured.

## RESULTS

The patients in this series did not have medial tumors. Extension onto the fundus of the internal auditory canal was present in all patients in both groups.

The histological slices showed little degeneration (mean 2%, range 0-10%), and there was no significant difference in this respect between the two groups. Iron was present in 95% of the slices of both groups. Because it was practically impossible to score the iron in the slices, this aspect could not be taken into consideration.

Since only small areas with degeneration were found, the surfaces with Antoni A and B cells were almost complementary. Statistical analysis showed a significant difference between the two groups with regard to the presence of Antoni A and Antoni B tumor areas. The tumors of patients with vestibular hypofunction appeared to contain significantly more Antoni B cell areas ($P=0.047$) and fewer Antoni A cell areas ($P=0.045$) compared to the tumors of patients with a normal vestibular function.

No significant difference in hearing loss was found between the two groups ($P=0.26$). However, statistical evidence for equality of the hearing levels of both groups is lacking because the number of patients in this study is too small. To demonstrate equal hearing levels, at least 36 pairs would have to be assessed (using a Schuirmann's two one-sided tests procedure), whereas the present study contained eight pairs.

## DISCUSSION

The histopathology of VSs is rather well known. Antoni wrote an extensive study on this topic in 1920 (3) in which he distinguished type A and type B cells, a distinction that remains valid. In most cases, type A tissue is sharply delimited from type B tissue, although sometimes the areas merge imper-

ceptibly (4). In this study, the areas with type A and B cells were fairly well demarcated in each tumor, allowing the quantification method to be applied successfully. In the primary group of patients described here, vestibular hypofunction appeared to be significantly correlated with a predominance of type B cells in the tumor. However, these findings, should be put in perspective. During VS surgery, it is unusual to resect the whole tumor for histopathologic examination. At least parts of the tumor are removed by surgical aspiration. Anyhow, the findings presented here may have several implications.

It is generally agreed that VSs may influence vestibular functioning by means of three mechanisms: compromising labyrinthine blood supply; changing the composition of inner ear fluids; and stretching or destroying of afferent axons (5). Previously, it was assumed that tumors arising from the inferior vestibular nerve are more apt to have a normal caloric response than those that originate in the superior vestibular nerve (6). Furthermore, about 90% of the VSs were said to arise from the superior vestibular nerve. However, both standpoints are highly debatable. First there is compelling evidence that the site of origin is evenly distributed over these two nerves (7). Secondly, in many cases it is virtually impossible to determine in which nerve the tumor has originated. Finally, a vestibular paresis is just as likely to accompany VSs arising from either nerve (8). Our findings suggest that the role of type A and type B cells should be considered as well. The distinction between type A and type B cells pertains not only to morphologic characteristics, but also to biologic behavior. The literature on this subject is rather scanty, however. In one study, Müller and Nasu investigated the presence of acid and alkaline phosphatase in VSs and found major similarities between the histopathology of a type B tumor and the process of Wallerian degeneration (9). Type B tissue contains relatively large amounts of fatty substance (10-12). This phenomenon is generally ascribed to degenerative changes, analogous to the fatty degeneration that takes place in the distal portion of a transected nerve. This could imply that a type B tumor is more

likely to result in blockage of vestibular pathways than a type A tumor would be. However, this resemblance to Wallerian degeneration seems very speculative and was denied by others (13). Compared to type A cells, type B cells contain significantly more organelles within the cytoplasm. Moreover, type B cells are characterized by the presence of a well-developed endoplasmatic reticulum and Golgi network. There is also an abundance of mitochondria, lysosomes, and membrane-bound osmophilic bodies. In particular, the presence of large aggregates of organelles and osmophilic material suggests that type B tissue is capable of a high degree of metabolic activity (14). In fact, type B cells have a more pronounced liquefactive action on a culture medium (15). In light of these observations, it is conceivable that a metabolic process in type B tissue could disturb the functional integrity of the axis cylinders. The results of this study indicate that a predominance of type B cells in a VS is significantly related to the presence of vestibular symptoms and not directly to hearing loss. Therefore, the vestibular symptoms probably do not come from the deranged composition of inner ear fluids; involvement of axons seems to be a more likely explanation. Type B tumors frequently contain multiple microcystic lesions. These microcysts may coalesce into larger cysts and give rise to a rapid increase in volume (15). This may lead to functional blockage of the axons of the vestibular nerves, which could explain why vestibular symptoms are more likely to occur in patients with type B lesions.

In conclusion, there are indications that type B cells behave differently than type A cells. The results of this study suggest that the development of a vestibular paresis in VS patients is enhanced by a functional discontinuity of the axons of the vestibular nerves. Presumably Antoni B cells play an important role in this process, although the exact pathogenetic mechanism remains unclear.

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# 6

# CHAPTER 6

## VESTIBULAR SCHWANNOMA: NEGATIVE GROWTH AND AUDIOVESTIBULAR FEATURES

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*(Submitted for publication)*

## ABSTRACT

At the University Medical Center Utrecht, a non-operative management was pursued in 44 patients with a unilateral vestibular schwannoma between 1990 and 1997. During that period, consecutive tumor sizes were determined by magnetic resonance imaging. Three of the 44 patients showed a significant decrease in tumor size. This study describes the initial vestibular status and the audiometric changes measured in the course of time in these 3 patients. Vestibular testing included the bithermal caloric test, the torsion test, the saccade test, the smooth pursuit test, and the registration of spontaneous nystagmus. Pure-tone and speech audiometry were performed at regular intervals. The 3 patients had a severe vestibular paresis on the affected side. Although the size of their tumor decreased, their hearing gradually deteriorated, just as it does in the majority of patients with a growing or stable vestibular schwannoma. The observations presented here suggest that the development of symptoms in a vestibular schwannoma is the result of the same pathogenetic mechanism, not only when the tumor is growing or stable but also when it is decreasing in size.

## INTRODUCTION

The number of patients identified with a vestibular schwannoma (VS) has been increasing since the advent of magnetic resonance imaging (MRI) [22]. Small intracanalicular tumors are more easily detected with MRI. In fact, the wider availability of this imaging technique has led to the identification of an increasing number of small tumors [5,13]. Moreover, asymptomatic VSs have been reported [4,26]. There is a tendency to adopt a conservative approach in the management of select patients with a VS. This stance is partly the result of an increasing number of longitudinal studies that demonstrate absence of growth in a considerable proportion of the patients [29]. Even negative growth has been reported in some of these studies [2,5,11,12,15,19], although this decrease in tumor size is not always precisely documented. It has been shown that only a few audiologic and vestibular parameters accompany tumor progression in VS patients [4,26]. To our knowledge, there is no literature on audiovestibular findings in patients with shrinking tumors. In that light, the aim of this study is twofold. First, we tried to quantify the decrease in tumor size in patients with a VS in whom we observed negative growth. Secondly, we assessed their initial vestibular status and followed several audiometric parameters over time.

### Case reports

Between 1990 and 1997, 44 patients, all of whom had characteristic signs and symptoms of a unilateral VS, were conservatively managed at the University Medical Center Utrecht. This conservative policy was adopted for various reasons: decision of the patient; age and/or poor physical condition of the patient; and the presence of a tumor in the better or only hearing ear. All patients underwent a neuro-otological examination as well as pure-tone and speech audiometry. The vestibular function was assessed by means of electronystagmographic registration during the bithermal caloric test, the

torsion test, the saccade test, and the smooth pursuit test. Procedures and normal values in this study are in accordance with internationally accepted guidelines [28]. MRI scans and audiometry were performed at yearly intervals.

This report pertains to 3 patients with a shrinking tumor. The size of the tumor was determined on the basis of MRI in the axial plane using 3 different methods. One was by taking the maximum extrameatal diameter parallel to the petrous ridge. Another was by calculating the surface of the maximum lesion depicted [24]. The third was by measuring the tumor size according to the guidelines of the American Academy of Otolaryngology-Head and Neck Surgery [1].

**Case 1**

A 39-year-old male was referred to our hospital because of vertigo of sudden onset. After 3 months his symptoms had disappeared. He had not noticed any hearing loss or tinnitus. There was no spontaneous nystagmus. Pure-tone audiometry revealed a high-frequency sensorineural hearing loss that amounted to 35 dB HL at 4.0 kHz (Table 1), and speech audiometry showed normal values (Table 2). Both the caloric test and the torsion test revealed a severe vestibular paresis (71%) on the right side with central compensation. The saccade test and the smooth pursuit test revealed no abnormalities. On MRI, a lesion with an extrameatal diameter of 18 mm was found. Because of the virtual absence of symptoms, the patient preferred conservative management. The follow-up period lasted 9 years. After that length of time, his hearing had deteriorated; in the pure-tone audiogram, it was scored at 2.0 and 4.0 kHz (Table 1). At speech audiometry, the maximum discrimination and the SRT seemed to have deteriorated as well, although to a minor degree (Table 2). There is clear evidence that the size of the tumor had decreased during the follow-up period, as demonstrated in Table 3 and Fig. 1.

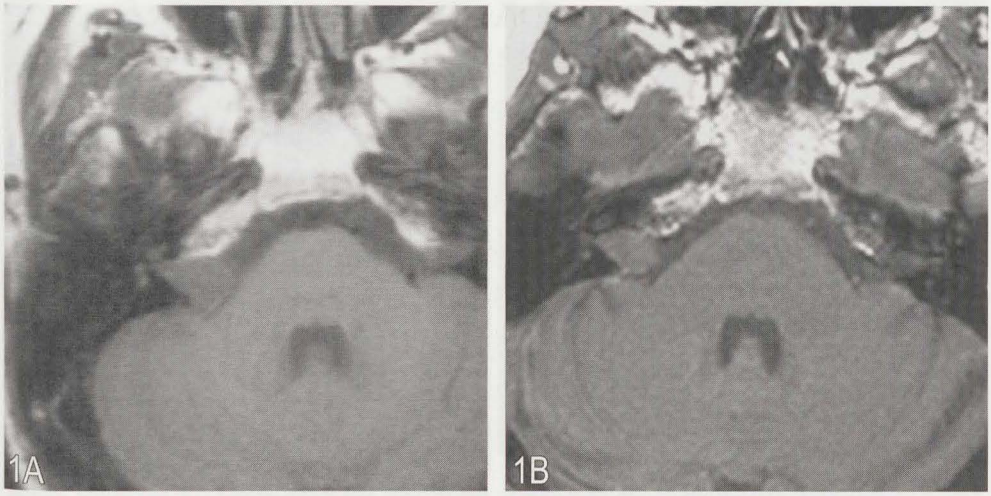


Fig. 1 Patient 1. MRI-scans in the axial plane; the images show the largest surface of the tumor, initially (A) and after 9 years follow-up (B). See also Table 3.
The images are printed on the same scale.

## Case 2

A 67-year-old female was referred to us because of a slowly progressive hearing loss without tinnitus. This symptom had been present for about 10 years. Six years before, she had experienced some signs of imbalance, but these had disappeared in a few days. Pure-tone and speech audiometry showed severe (sensorineural) hearing loss on the left side (Tables 1 and 2). Vestibular examination showed a left-sided vestibular paresis (80%) with central compensation. There was no spontaneous nystagmus, and both the saccade test and the smooth pursuit test were normal. On MRI, a VS of 20 mm was found. In view of the protracted history, the relatively small tumor size, and the advanced age of the patient, it was decided to pursue conservative management. She was followed for 10 years. During that period, her audiometric parameters had deteriorated, as shown in Tables 1 and 2. It is obvious that the tumor size had decreased (Table 3, Fig.2).

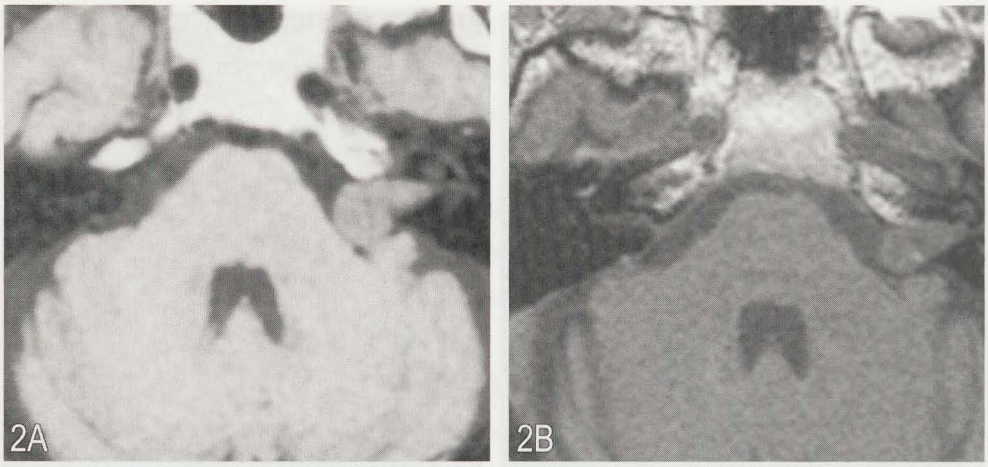


Fig. 2 Patient 2. MRI-scans in the axial plane; the images show the largest surface of the tumor, initially (A) and after 10 years follow-up (B). See also Table 3.
The images are printed on the same scale.

## Case 3

A 69-year-old female had a left-sided progressive hearing loss for about 1 year. She also complained of a high-frequency tinnitus on that side. Pure-tone audiometry showed a rather severe sensorineural hearing loss in the left ear, which was more pronounced at the high frequencies (Table 1). The findings at speech audiometry also indicated a serious hearing impairment on the affected side (Table 2). Vestibular examination showed a vestibular paresis (38%) on this side with central compensation. There was no spontaneous nystagmus, and both the saccade test and the smooth pursuit test revealed no abnormalities. MRI showed a VS of 15 mm. Her advanced age was the main reason to adopt a conservative management. She was followed for 4 years. In that period, the size of the tumor decreased (Table 3, Fig. 3), whereas her hearing had deteriorated (Tables 1 and 2).

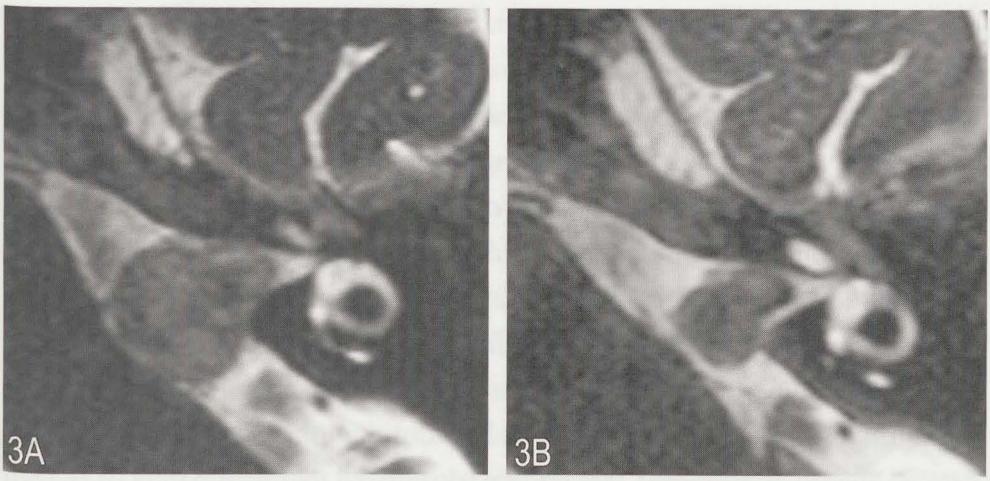


Fig. 3 Patient 3. MRI-scans in the axial plane; the images show the largest surface of the tumor, initially (A) and after 4 years follow-up (B). See also Table 3.
The images are printed on the same scale.

| | Patient 1 | | Patient 2 | | Patient 3 | |
|---|---|---|---|---|---|---|
| | Initial | Follow-up (9 yrs.) | Initial | Follow-up (10 yrs.) | Initial | Follow-up (4 yrs.) |
| 0.5 kHz | 10 | 10 | 75 | 85 | 60 | 70 |
| 1.0 kHz | 15 | 15 | NR | NR | 65 | 70 |
| 2.0 kHz | 10 | 20 | NR | NR | 70 | 90 |
| 4.0 kHz | 35 | 50 | NR | NR | 85 | 100 |

Table 1 Initial thresholds and the thresholds (in dB HL) after the follow-up periods in the pure-tone audiogram at the frequencies 0.5, 1.0, 2.0 and 4.0 kHz of the patients. The data pertain to the affected side. NR = No Response.

## DISCUSSION

Overall progressive sensorineural hearing loss is a characteristic symptom in patients with a VS [21]. Interestingly, all 3 patients described here also had a gradually progressive hearing loss. Loss at the high frequencies is the most common type of hearing impairment in VS patients [3,9,17]. Indeed, the 3 patients reported here had a classic down-sloping audiogram showing more pronounced losses in the high frequency ranges. Thus, the thresholds at pure-tone audiometry in these 3 patients did not differ from those found in the majority of other VS patients. Nor did they differ with regard to the data on speech audiometry. It is widely recognized that parameters of speech audiometry are generally worse than could be expected on the basis of the thresholds in the pure-tone audiogram [27]. This discrepancy was found in 2 of these 3 patients as well. In Patient 2, the initial examination revealed a complete absence of speech discrimination in combination with residual hearing at the low frequencies, as assessed by pure-tone audiometry. In Patient 3, there is a striking discrepancy between the thresholds in the pure-tone audiogram on the one hand, and the parameters of speech audiometry,

| | Patient 1 | | Patient 2 | | Patient 3 | |
|---|---|---|---|---|---|---|
| | Initial | Follow-up (9 yrs.) | Initial | Follow-up (10 yrs.) | Initial | Follow-up (4 yrs.) |
| SRT (dB SPL) | 10 | 15 | - | - | 70 | - |
| Maximum discrimination (%) | 100 | 97 | 20 | 0 | 66 | 33 |
| Loudness (dB SPL) | 70 | 75 | 120 | 120 | 100 | 100 |

Table 2 Outcomes of speech audiometry: the speech reception threshold (SRT) and the maximum discrimination with the corresponding loudness of the 3 patients before and after the follow-up periods. The data pertain to the affected side.

on the other. It can be concluded that the above - mentioned audiometric data on the patients with shrinking tumors are in accordance with the classic clinical picture of patients with a VS: a. the hearing loss was slowly progressive; b. there was a down-sloping curve at pure-tone audiometry; and c. there was disproportionality between the ability to understand speech and the ability to perceive pure tones in 2 of these 3 patients.

All 3 patients had a vestibular paresis, as ascertained by means of bithermal caloric stimulation. The data in the literature suggest the presence of a reduced caloric response in the majority of the patients [7,10,16,25]. Furthermore, the literature reveals that symptoms of dizziness are usually either mild and transient or completely absent. That profile fits the patients described here: 2 patients had a history of mild and transient symptoms of vertigo, whereas 1 patient did not have such complaints. We conclude that the patients with shrinking tumors, as reported here, also have vestibular signs and symptoms that are not different from those found in the majority of other patients with a VS.

The literature on shrinkage of VSs is both sparse and speculative. Some

| | Patient 1 | | Patient 2 | | Patient 3 | |
|---|---|---|---|---|---|---|
| | Initial tumor size | Size after follow-up (9 yrs.) | Initial tumor size | Size after follow-up (10 yrs.) | Initial tumor size | Size after follow-up (4 yrs.) |
| Maximum diameter (mm) | 18 | 15 | 19 | 16 | 20 | 15 |
| Maximum surface (mm2) | 146 | 112 | 168 | 119 | 163 | 98 |
| Size according to AAO-HNS (mm) | 13.5 | 11.5 | 14.5 | 12.0 | 16.5 | 13.5 |

Table 3 The size of the tumors, calculated according to 3 methods, before and after the follow-up periods.

have postulated that degenerative changes with fibrosis may shrink the tumor. A hemorrhage is thought to be responsible for these degenerative changes [6,8,11,14]. Another explanation may be a disruption of the external blood supply to the tumor. Furthermore, there is evidence that VSs tend to grow more slowly in older persons [11,14,23]. In that light, it has been hypothesized that shrinkage is partially an age-related phenomenon [18]. These explanations are all very tentative, however, since there is no validation. There have been no histological examinations of specimens of tumors with a documented history of negative growth, simply because surgery is not a realistic option in these patients. Audiovestibular symptoms in patients with a VS may result from any of the following: a. blockage of afferent nerve fibers; b. compromised blood supply to the cochleovestibular system; or c. a change in the composition of inner-ear fluids [20]. Actually, the symptoms are possibly due to a combination of these 3 factors. The observations presented here suggest that the development of symptoms in VS patients is the result of the same pathogenetic mechanism. This seems to be the case not only when the tumor is growing or stable but also when it is decreasing in size.

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# 7

# CHAPTER 7

## SUMMARY AND CONCLUSIONS
## SAMENVATTING EN CONCLUSIES

## SUMMARY AND CONCLUSIONS

The studies comprising this thesis deal with the biological behavior of vestibular schwannomas (VSs), generally called acoustic neuromas (ANs). In chapter 2, we use the term AN for editorial reasons; in the other chapters, we use the term VS. All of the studies presented here were performed at the University Medical Centre Utrecht.

A VS is a benign tumor. It arises from Schwann cells of the superior or inferior part of the vestibular portion of the eighth cranial nerve. The tumor usually originates in the internal auditory canal and may expand into the cerebellopontine angle and posterior fossa. In the course of the disease, symptoms such as unilateral sensorineural hearing loss, tinnitus, or vertigo occur. If the disease progresses, serious, eventually life-threatening, neurological symptoms can arise. Even so, it proves that VSs grow at very different rates. Tumors that grow rapidly will almost always require treatment. Slowly growing tumors, in contrast, may not. In that light, studies of the natural behavior of a VS ultimately seek to identify factors to predict how quickly it will grow, how the symptoms will progress, and how it will harm the patient. Insight into its natural behavior could affect the choices for therapy. This is very important in clinical practice, as any treatment – whether surgery or radiotherapy – entails some risk of morbidity.

### Ipsi- and contralateral hearing loss with a VS

Usually, the first symptom of a VS that the patient notices is unilateral sensorineural hearing loss. In most cases, audiometry gives the first indication of a tumor; proof is then provided by magnetic resonance imaging (MRI). Chapter 2 presents audiometric findings in a group of 171 patients with a unilateral VS. In that study, the results of tone and speech audiometry are related to the sort and duration of symptoms and to the size of the tumor. First of all, there seems to be no significant correlation between hearing loss and tumor size. This finding was not surprising, as it conforms to the results

of other studies. Second, the extent of hearing loss shows a significant positive correlation with the subjective duration of this hearing loss. The general assumption that VS is a slowly progressive disease seems to be confirmed by this finding. Third, hearing on the contralateral side is worse than in the normal population. Fourth, the women in the study were significantly older than the men at the time they were diagnosed. These last two findings may be explained by the fact that not all VS patients are diagnosed as such; it is probable that not all VSs are detected. Because patients with concomitant hearing loss on the contralateral side are likely to seek medical advice at an earlier stage, VSs are more likely to be detected in that group. Furthermore, women tend to live longer than men. If we assume that men and women are equally susceptible to this disease, there is more chance for a VS to be detected in a woman. Probably because of women's longer life expectancy, the average age at which a VS is detected is higher in women than in men. The fact that women have better hearing than men might also be a factor.

**Tumor size and vestibular examination**

Between 1986 and 1996, 121 patients with a unilateral VS were given vestibular examinations. Chapter 3 describes the correlations between the parameters used in that examination and the size and growth of the tumor. In this retrospective study, the notion of 'tumor progression' was introduced as a measure of tumor size. It is defined as the quotient of tumor size and duration of symptoms. First of all, 79% of the patients had a vestibular paresis at caloric testing. The larger the tumor, the more severe their paresis. Due to the wide range of normal values recorded for the caloric test, we could not detect small changes in vestibular response. Caloric testing seems to be more sensitive when used to detect larger tumors. Second, the results of the torsion test show that the larger the tumor, the smaller the gain. A fast-growing or biologically active tumor will probably produce vestibular asymmetry because central compensation does not occur in time (or not sufficiently). Therefore, we expected that patients with a growing tumor would show

a directional preponderance to the contralateral side in both the caloric and the torsion test. However, we did not find this to be the case. One reason might be that this retrospective study lacked a good measure of tumor growth. Another reason might be that central compensation could actually take place. A third finding is that 29 patients had a spontaneous nystagmus. Their tumors were significantly larger than the ones in patients who did not have a spontaneous nystagmus. The slow component velocity of this nystagmus correlated significantly with tumor size and tumor progression. Thus, a labyrinthine hypofunction found by caloric testing, in combination with a smaller gain in the torsion test, would seem to indicate the presence of a large VS. Furthermore, a spontaneous nystagmus also seems to be indicative of a large tumor.

**Tumor size in a longitudinal study: a new measuring protocol**

MRI is the most sensitive tool for detection of a VS. It is also the best means to estimate the size of the tumor. Chapter 4 presents the results of a longitudinal study of patients who were not given therapy, for various reasons. MRI was used to establish any changes in tumor size, which was estimated by taking the maximum extrameatal diameter in the axial plane. A neuroradiologist and an otorhinolaryngologist each made an independent estimate of every scan. Later, these images were analyzed again by measuring the maximum surface of a cross-section through the tumor in the axial plane. The reason to perform a retrospective analysis was to replace the subjective assessment by an objective method that would yield a number as a measure of tumor size. As it turns out, the results of both methods were highly consistent. Thus, we conclude that the new measuring method is just as reliable as the assessment made by the clinicians.

Between 1990 and 1997, we followed up on 44 patients. The size of their tumors was assessed at regular intervals by analyzing MRI images. Each of these 44 patients had signs, symptoms, and MRIs that were characteristic of a unilateral VS. The patients were followed for an average of 3.5 years

(range 2-7 years). An MRI was performed 3.7 times, on average (range 2-7 times). In eight patients (18%), the tumor size increased; in three (7%), the tumor got smaller; and 33 tumors (75%) showed no significant change in size. We tried to compare these results with findings from other longitudinal studies. However, outcomes reported in the literature are not based on a uniform measuring method. Moreover, many studies combine different kinds of imaging techniques in one series and then compare the results. Though lacking a firm basis for comparison, we nonetheless conclude that the percentage of non-growing tumors that we found may be considered relatively high. Further studies are needed, especially studies spanning longer periods, to substantiate our findings on the growth pattern of a VS.

**Positive correlation between predominance of Antoni type B cells and vestibular paresis**

Chapter 5 presents the histological characteristics of patients with a normal vestibular function and patients with vestibular paresis. The vestibular examination of 121 patients, as described in chapter 3, revealed eight patients with a normal vestibular function. Each patient was matched with a patient who had a tumor of equal size but who also had vestibular paresis. Then, the ratio of Antoni type A and Antoni type B cells was studied in the histological slides of the peroperatively obtained material. The tumors of patients with vestibular paresis proved to contain significantly more type B cells. Therefore, we conclude that the cell types in a VS differ not only morphologically but also biologically. In light of data in the literature on the histology of VSs, we may assume that type B cells will lead to a discontinuity in vestibular pathways sooner than type A cells. This suggests that vestibular paresis in VS patients is mainly caused by a functional discontinuity in the vestibular nerves. Thus, besides tumor size, the histological composition of the tumor also seems to play a role in the incidence of vestibular paresis.

**A report on three 'shrinking' tumors**

Three of the patients enrolled in the longitudinal study, as described in chapter 4, proved to have a tumor that got smaller over time. The initial vestibular status and the audiometric changes in the course of time are reported in chapter 6. The pure-tone audiogram revealed that two of these patients had severe sensorineural hearing loss, especially at higher frequencies. The other patient had a slight sensorineural hearing loss at 4 kHz. Vestibular examination revealed a compensated vestibular paresis of the affected side. The three patients were followed for 4, 9, and 10 years, respectively. In all of them, the tumor had decreased in size, as shown on the MRI images. Over the same period, the hearing loss on the affected side increased. The audiovestibular symptoms of the patients with a shrinking tumor do not seem to differ from the symptoms of patients whose tumor was stable or growing; all had symptoms that are characteristic of a VS. This might mean that symptoms of a VS are caused by a pathogenetic mechanism that is at least partially independent of changes in the size of the tumor.

# SAMENVATTING EN CONCLUSIES

De onderzoeken beschreven in dit proefschrift richten zich op een aantal aspecten van het biologische gedrag van het vestibulair schwannoom ("vestibular schwannoma",VS), meer bekend onder de naam acusticus-neurinoom ("acoustic neuroma", AN). In hoofdstuk 2 wordt - om redactionele redenen - in tegenstelling tot in de andere hoofdstukken, de term AN gebruikt. Overigens wordt gesproken van VS. Alle hier beschreven studies zijn verricht in het Universitair Medisch Centrum Utrecht.
Het VS is een benigne tumor uitgaande van de Schwann-cellen van de nervus vestibularis. De tumor ontstaat meestal in de inwendige gehoorgang en kan zich vervolgens uitbreiden naar de brughoekregio. In het verloop van de ziekte kunnen progressieve verschijnselen ontstaan, zoals eenzijdig perceptief gehoorverlies, tinnitus en/of evenwichtsklachten. Bij verdere progressie van de tumor kunnen ernstige, uiteindelijk zelfs levensbedreigende, neurologische symptomen optreden. Het blijkt echter dat de groeisnelheid van het VS zeer verschillend kan zijn. Snel groeiende tumoren vereisen vrijwel altijd behandeling. Echter, ten aanzien van zeer langzaam groeiende tumoren doet zich de vraag voor of therapie noodzakelijk is. Het uiteindelijke doel van onderzoek naar het natuurlijke gedrag van de tumor is de identificatie van voorspellende factoren voor groei van de tumor, progressie van symptomen en schade voor de patiënt. Meer inzicht in het biologische gedrag van de tumor kan dus consequenties hebben voor het therapeutisch beleid. Dit is van groot belang omdat elke behandeling - dus zowel operatie als radiotherapie - een zekere kans op morbiditeit inhoudt.

## Ipsi- én contralateraal gehoorverlies bij het VS

Eenzijdig perceptief gehoorverlies is meestal het eerste symptoom dat door de patiënt wordt bemerkt. Voordat kernspintomografie ("magnetic resonance imaging", MRI) uiteindelijk tot het bewijs van de aanwezigheid van de tumor leidt, levert audiometrie derhalve in de meeste gevallen de eerste aan-

wijzing daarvoor. In hoofdstuk 2 wordt verslag gedaan van de audiometrische bevindingen bij 171 patiënten met een eenzijdig VS. De resultaten van toon- en spraakaudiometrie werden vergeleken met de aard en duur van symptomen en de grootte van de tumor. Ten eerste bleek geen significante correlatie te bestaan tussen de mate van het gehoorverlies en de tumorgrootte. Dit was niet onverwacht omdat het overeenkomt met de resultaten van andere studies. Ten tweede werd wel een significante positieve correlatie tussen de mate van het gehoorverlies en de subjectieve duur van het gehoorverlies gevonden. De algemene aanname dat het VS een langzaam progressieve aandoening is, lijkt hiermee bevestigd. Ten derde bleek het gehoor aan de contralaterale zijde slechter dan in de normale populatie en ten vierde bleken vrouwen in de onderzochte groep op het moment dat de diagnose werd gesteld een significant hogere leeftijd te hebben dan mannen. De twee laatste bevindingen berusten waarschijnlijk op het verschijnsel dat patiënten bij wie een VS is vastgesteld slechts een deel vormen van alle patiënten met een VS (het is aannemelijk dat een deel van de tumoren niet wordt ontdekt). Patiënten met een begeleidend gehoorverlies aan de contralaterale zijde zoeken waarschijnlijk eerder medische hulp en de kans dat bij hen dan een VS wordt ontdekt is dus groter dan bij patiënten met een normaal gehoor aan de contralaterale zijde. Vrouwen leven in het algemeen langer dan mannen. Wanneer we ervan uitgaan dat het VS even vaak bij mannen als bij vrouwen ontstaat, is de kans dat bij vrouwen een VS wordt ontdekt dus groter. De gemiddelde leeftijd waarop de tumor wordt ontdekt, ligt bij vrouwen hoger waarschijnlijk als gevolg van hun hogere levensverwachting. Ook het feit dat het gehoor bij vrouwen beter is dan bij mannen speelt hierbij mogelijk een rol.

**Tumorgrootte en evenwichtsonderzoek**

Bij 121 patiënten die tussen 1986 en 1996 in verband met een eenzijdig VS gezien zijn, is een uitgebreid evenwichtsonderzoek verricht. In hoofdstuk 3 is gekeken of een samenhang bestaat tussen een aantal parameters van dit

evenwichtsonderzoek en de grootte en groei van de tumor. Om in deze retrospectieve studie een maat te hebben voor groei werd het begrip tumorprogressie geïntroduceerd. Dit werd gedefinieerd als het quotiënt van de tumorgrootte en de duur van de klachten. In de eerste plaats werd bij het calorisch onderzoek bij 79% van de patiënten een vestibulaire hypofunctie gevonden. Deze hypofunctie bleek ernstiger naarmate de tumor groter was. In de tweede plaats bleek dat bij het pendelstoelonderzoek de gain afnam naarmate de tumor groter was. Bij snel optredende vestibulaire asymmetrie als gevolg van de aanwezigheid van een snel groeiende of biologisch actieve tumor zal naar verwachting centrale compensatie niet op tijd of onvolledig plaats vinden. Wij verwachtten derhalve bij calorisch onderzoek of pendelstoelonderzoek een nystagmusvoorkeur te vinden naar de contralaterale zijde. In ons onderzoek kon dit echter niet worden aangetoond, mogelijk doordat er in deze retrospectieve studie geen goede maat was voor groei, dan wel doordat het vestibulaire compensatieproces de gevolgen van eventuele groei en progressie van de tumor kon bijhouden. In de derde plaats werd bij 29 patiënten een spontane nystagmus geconstateerd. Bij deze patiënten was de tumor significant groter dan bij de patiënten zonder spontane nystagmus. De snelheid van de langzame fase van deze nystagmus correleerde significant met de tumorgrootte en de tumorprogressie. Bovenstaande suggereert dat een hypofunctie gevonden in het calorigram, in combinatie met een lage gain bij het pendelstoelonderzoek, een indicatie is voor de aanwezigheid van een groot VS. Ook de aanwezigheid van een spontane nystagmus duidt op een grote tumor.

**Tumorgrootte in een longitudinale studie, vastgelegd met een nieuwe meetmethode**

MRI is de meest sensitieve methode om een VS te detecteren en de beste methode om een indruk te krijgen van de tumorgrootte. In hoofdstuk 4 worden de resultaten beschreven van een longitudinale studie bij patiënten die in eerste instantie om verschillende redenen niet in aanmerking kwamen

voor behandeling. Eventuele veranderingen van de tumorgrootte werden vastgesteld met MRI aan de hand van een schatting van de maximale extrameatale diameter in het axiale vlak. Dit werd telkens gedaan door een neuroradioloog en een KNO-arts onafhankelijk van elkaar. Retrospectief werden deze beelden opnieuw geanalyseerd. Hierbij werd het maximale oppervlak van de doorsnede van de tumor in het axiale vlak gemeten. Dit werd gedaan om de hierboven beschreven subjectieve methode te vervangen door een objectief onderzoek waarmee wij over een getal beschikten als maat voor de grootte van de tumor. De resultaten van beide methoden kwamen goed overeen. Hieruit wordt geconcludeerd dat de toegepaste meetmethode net zo betrouwbaar is als de beoordeling door clinici. Tussen 1990 en 1997 werden 44 patiënten gecontroleerd, waarbij de afmetingen van de tumor met regelmatige intervallen werden bepaald aan de hand van beelden verkregen met MRI. Bij elk van deze 44 patiënten was er sprake van klachten, symptomen en MRIs die karakteristiek waren voor de aanwezigheid van een enkelzijdig VS. De patiënten werden gedurende gemiddeld 3,5 jaar (spreiding 2-7 jaar) gecontroleerd, waarbij gemiddeld 3,7 maal (spreiding 2-7 maal) MRI werd verricht. De tumorgrootte nam bij 8 patiënten (18%) toe, 3 tumoren (7%) namen in grootte af en 33 tumoren (75%) toonden geen significante verandering. Getracht werd deze resultaten te vergelijken met andere longitudinale studies in de literatuur. Dit bleek niet goed mogelijk doordat enerzijds een uniforme meetmethode ontbrak en anderzijds doordat de meeste gegevens in de literatuur van betrekkelijk geringe waarde zijn. Het laatste is het gevolg van het feit dat in veel onderzoeken de resultaten van verschillende beeldvormende technieken tot één serie worden samengevoegd en dan met elkaar worden vergeleken. Niettemin is het door ons gevonden percentage niet groeiende tumoren verhoudingsgewijs hoog. Verder onderzoek, met name over langere perioden, zal meer zekerheid kunnen verschaffen over het groeipatroon van het VS.

**Positieve correlatie tussen de overheersing van Antoni B cellen en vestibulaire uitval**

In hoofdstuk 5 worden histologische kenmerken beschreven van tumoren van patiënten met een normaal functionerend labyrint en van tumoren van patiënten met een uitgevallen labyrint. Op grond van het vestibulaire onderzoek bij de 121 patiënten, beschreven in hoofdstuk 3, werden 8 patiënten gevonden bij wie sprake was van een normale vestibulaire functie. Elk van deze patiënten werd vergeleken met een patiënt die een tumor van dezelfde afmeting had met vestibulaire uitval. In de histologische coupes van het peroperatief verkregen materiaal werd gekeken naar de verhouding tussen de hoeveelheid Antoni type A en Antoni type B weefsel. De tumoren van patiënten met een vestibulaire uitval bleken significant meer type B weefsel te bevatten. Op grond hiervan wordt gesteld dat er aanwijzingen zijn dat de weefseltypen in het VS niet alleen in morfologisch opzicht verschillen maar zich ook biologisch anders gedragen. Gegevens in de literatuur over de histologie van het VS geven aanleiding te veronderstellen dat Antoni type B weefsel eerder dan type A weefsel aanleiding geeft tot onderbreking van vestibulaire banen. Dit laatste suggereert dat vestibulaire uitval bij patiënten met een VS vooral ontstaat als gevolg van een functionele discontinuïteit van de nervi vestibulares. Behalve de tumorgrootte lijkt ook de histologische samenstelling van de tumor een rol te spelen.

**Rapportage van drie "krimpende" tumoren**

Drie van de patiënten uit de longitudinale studie, beschreven in hoofdstuk 4, bleken een tumor te hebben die in de loop van de tijd in grootte afnam. De resultaten van het initiële vestibulaire onderzoek en het beloop in de tijd van een aantal audiologische parameters bij deze patiënten zijn beschreven in hoofdstuk 6. Twee van de patiënten hadden een aanzienlijk perceptief gehoorverlies in het toonaudiogram, vooral in de hoge frequenties. Bij één patiënt was er slechts een gering perceptief verlies bij 4 kHz. Het vestibulaire onderzoek toonde aan dat bij deze drie patiënten sprake was van een

gecompenseerde labyrintaire uitval aan de aangedane zijde. De patiënten werden respectievelijk 4, 9 en 10 jaar vervolgd. In die periode nam bij elk van hen de tumorgrootte af blijkens de beelden verkregen met MRI. Het gehoorverlies nam aan de aangedane zijde toe. De audiovestibulaire symptomen bij deze patiënten met een krimpende tumor lijken dus niet te verschillen van de symptomen die bij de meerderheid van de patiënten met een in grootte stabiel of groeiend VS worden beschreven en die als karakteristiek voor het VS worden beschouwd. Bovenstaande zou erop kunnen wijzen dat symptomen bij het VS veroorzaakt worden door een pathogenetisch mechanisme dat minstens ten dele onafhankelijk is van veranderingen in de grootte van de tumor.

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## CURRICULUM VITAE

De auteur van dit proefschrift werd geboren op 28 februari 1964 te Den Haag. In 1982 behaalde zij het eindexamen OVWO aan de Rijswijkse Openbare Scholengemeenschap. Na een jaar psychologie begon zij in 1983 aan de studie geneeskunde aan de Rijksuniversiteit Leiden. Het artsexamen werd in 1992 behaald.
Vervolgens werkte zij gedurende 11 maanden als arts-assistent chirurgie (AGNIO) in het Carolus-Liduina Ziekenhuis te 's-Hertogenbosch. Hierna was zij twee jaar werkzaam als arts-assistent (AGNIO) Keel-, Neus - en Oorheelkunde in het Centraal Militair Hospitaal te Utrecht. In 1995 begon zij als AGNIO KNO in het Academisch Ziekenhuis Utrecht. Sinds 1996 is zij hier in opleiding tot KNO-arts (Prof. Dr. E.H. Huizing, Prof. Dr. G.J. Hordijk). De B-opleiding werd gevolgd in het Ziekenhuiscentrum Apeldoorn (J.B. Antvelink). Zij zal in 2001 deze opleiding voltooien.

De auteur is getrouwd met Jelle Wissmann. Zij hebben twee kinderen, Britt en Hidde.