Risk factors and analysis of long-term headache in sporadic vestibular schwannoma: a multicenter cross-sectional study

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OBJECT The primary goals of this study were: 1) to examine the influence of disease and treatment on headache in patients with sporadic vestibular schwannoma (VS); and 2) to identify clinical predictors of long-term headache disability.

METHODS This was a cross-sectional observational study with international multicenter enrollment. Patients included those with primary sporadic < 3-cm VS and a separate group of general population control subjects without tumors. Interventions included a postal survey incorporating the Headache Disability Inventory (HDI), the Hospital Anxiety and Depression Scale, and a VS symptom questionnaire. The main outcome measures were univariate and multivariable associations with HDI total score.

RESULTS The overall survey response rate was 79%. Data from 538 patients with VS were analyzed. The mean age at time of survey was 64 years, 56% of patients were female, and the average duration between treatment and survey was 7.7 years. Twenty-seven percent of patients received microsurgery, 46% stereotactic radiosurgery, and 28% observation. Patients with VS who were managed with observation were more than twice as likely to have severe headache disability compared with 103 control subjects without VS. When accounting for baseline differences, there was no statistically significant difference in HDI outcome between treatment modalities at time of survey. Similarly, among the microsurgery cohort, the long-term risk of severe headache disability was not different between surgical approaches. Multivariable regression demonstrated that younger age, greater anxiety and depression, and a preexisting diagnosis of headache were the primary predictors of severe long-term headache disability, while tumor size and treatment modality had little influence.

CONCLUSIONS At a mean of almost 8 years following treatment, approximately half of patients with VS experience headaches of varying frequency and severity. Patient-driven factors including age, sex, mental health, and preexisting headache syndrome are the strongest predictors of long-term severe headache disability. Tumor size and treatment modality have less impact. These data may assist with patient counseling regarding long-term expectations following diagnosis and treatment.

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OVER the last 100 years, the treatment of vestibular schwannoma (VS) has undergone tremendous evolution.³² With the increasing use of less invasive management methods including observation, stereotactic

radiosurgery (SRS), or radiotherapy and subtotal or near-total resection, incidences of disease-associated mortality, stroke, and permanent facial neuropathy have been substantially reduced.^{12,27,32,41} Given this, many investigators

ABBREVIATIONS CPA = cerebellopontine angle; HADS = Hospital Anxiety and Depression Scale; HDI = Henry Ford Hospital Headache Disability Inventory; HRQOL = health-related quality of life; ICHD-II = International Classification of Headache Disorders, Second Edition; IQR = interquartile range; PANQOL = Penn Acoustic Neuroma Quality of Life; SRS = stereotactic radiosurgery; VS = vestibular schwannoma.

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have begun analyzing patient-reported outcome measures in an effort to further define disease-related morbidity and to examine the effects of treatment.^{11,27}

Previous studies have demonstrated that among patients with sporadic VS, ongoing dizziness and headache are associated with the greatest health-related quality of life (HRQOL) reduction, whereas the contributions of unilateral hearing loss, tinnitus, and facial neuropathy are generally less by comparison.^{2-4,22,26} Despite the substantial physical and emotional burden associated with headache in patients with VS, this condition remains understudied. To our knowledge, no publications have specifically characterized headache in patients with VS receiving SRS or conservative observation. Additionally, there have been no studies in the surgical literature that have used validated headache disability inventories.

In a recent study, we evaluated long-term HRQOL outcomes between patients who were treated with microsurgery, SRS, and observation, using 3 generic measures and a recently validated disease-specific instrument, the Penn Acoustic Neuroma Quality of Life (PANQOL) scale.⁵ We found that the greatest reduction of HRQOL resulted from the disease itself, while long-term differences between treatment modalities were generally small. Only 3 of the 7 PANQOL domains demonstrated a statistically significant difference during global comparison: facial function, balance, and pain, with the latter exhibiting the largest difference between treatment arms. Although the 26-item PANQOL scale was found to be superior to other multipurpose HRQOL inventories at analyzing differences between treatment groups, it should be noted that the PANQOL scale uses only one question to determine pain outcome.

The current study sought to further characterize features of headache in a large multicenter cohort of patients with sporadic VS by using a validated headache disability inventory. First, a comparison of headache parameters was performed between a cohort of patients who were conservatively observed and a cohort of control patients without tumors to elucidate the contribution of disease alone on long-term headache. Second, a comparison of headache outcomes between patients who received observation, SRS, and microsurgery was performed to determine the influence of treatment modality on headache disability inventory scores. Last, pretreatment clinical variables were analyzed to determine high-risk features associated with long-term headache disability among all patients with VS.

Methods

Inclusion/Exclusion Criteria and Data Acquisition

Following institutional review board approval, all patients with VS who were evaluated between 1998 and 2008 at 2 independent tertiary medical centers were examined. All adult patients (≥ 18 years old) with primary sporadic small- to medium-sized (< 3 cm) VS were identified. Patients with neurofibromatosis Type 2, those who received treatment before 1998, patients who required more than one form of treatment (e.g., SRS after microsurgery), patients with tumors > 3 cm, and patients under the age of 18 years were excluded. Clinical data regarding patient demographics, tumor size, presence of hydrocephalus, and treatment parameters were collected. Tumor size

was classified according to the 1995 American Academy of Otolaryngology-Head and Neck Surgery guidelines.⁷

Eligible patients were surveyed with a postal questionnaire containing the Henry Ford Hospital Headache Disability Inventory (HDI), the Hospital Anxiety and Depression Scale (HADS), and a VS symptom questionnaire.^{18,48} Additionally, a population of adult nontumor controls was surveyed for comparison. The latter group was identified from a contact list purchased from a survey research firm (Marketing Systems Group). All US survey respondents were given monetary remuneration of 30 US dollars. All initial nonresponders received one additional follow-up letter or phone call regarding study participation.

Description of Validated Patient-Reported Outcome Measures

The HDI was developed and validated by Jacobson et al. in 1994 to assess the impact of headache on daily life and to determine response to treatment.¹⁸ The HDI is a 25-item instrument that requires patients to select from 1 of 3 responses for each question, including “yes,” “sometimes,” and “no,” with 4, 2, and 0 points assigned, respectively. Thus, the maximum (worst) score is 100 and the lowest (best) score is 0.

The HADS was developed by Zigmond and Snaith in 1983 to assess the severity of anxiety, depression, and emotional distress in a medical outpatient setting and to determine progress with therapy.⁴⁸ Several subsequent validation studies have confirmed good internal consistency and external validity.^{16,31,40} Each of the 14 items includes 4 ordinal responses, each scored on a scale of 0–3 points. Thus, the maximum (worst) possible total score is 42 and the lowest (best) possible score is 0.

Statistical Analysis

Continuous features were summarized with means, medians, and interquartile ranges (IQRs); categorical features were summarized with frequency counts and percentages. Sample sizes for features with missing data are indicated in italics in parentheses in tables. Since nearly half of the patients studied had HDI total scores of 0, the HDI was analyzed as > 0 versus 0 to identify associations with patients with any degree of headache disability (Fig. 1). The HDI was also analyzed as > 14 (i.e., the 75th percentile of the distribution of HDI total scores) versus ≤ 14 to identify associations with patients with severe headache disability. Associations with HDI total scores > 0 and > 14 were evaluated using logistic regression models and summarized with odds ratios and 95% confidence intervals. Multivariable models were developed using stepwise selection, with the *p* value for a feature to enter or leave the model set to 0.05. Comparisons between patients with VS who were observed and nontumor controls were evaluated using Wilcoxon rank-sum and chi-square tests. Comparisons of features among the SRS, observation, and microsurgery groups were evaluated using Kruskal-Wallis, chi-square, and Fisher exact tests. If the *p* value from a global test among the 3 groups was statistically significant, pairwise comparisons were evaluated using Wilcoxon rank-sum, chi-square, and Fisher exact tests. Statistical analyses were performed using the SAS software package (SAS

FIG. 1. Skewed distribution of HDI total score among 538 patients with sporadic VS.

Institute). All tests were 2-sided and p values < 0.05 were considered statistically significant.

Results

Population Overview

Data from 538 respondents were received and analyzed; 276 (51%) were from the US and 262 (49%) were from Norway. Seventy-nine percent of patients treated for VS who were successfully contacted returned a completed questionnaire set. Overall, the average age at time of survey was 64 years, 56% were women, and the mean time interval between treatment and survey was 7.7 years. Seventy-one percent of tumors demonstrated varying degrees of cerebellopontine angle (CPA) extension, whereas the remaining 29% were confined to the internal auditory canal. One hundred forty-three (27%) patients received microsurgery, 247 (46%) SRS, and 148 (28%) conservative observation (Fig. 2). Additionally, data from 103 nontumor control subjects were analyzed. Sixty percent of patients with VS reported having headaches prior to treatment, and 19% had an established diagnosis of migraine. Overall, 15% thought that their headaches worsened following treatment, 14% believed that they had experienced improvement, and 70% did not perceive an appreciable change (Table 1).

Impact of Disease on Headache

A comparison of clinical features between 148 patients with observed VS and 103 nontumor controls was performed (Table 2). The control group was younger and there was a trend toward poorer HADS total scores compared with the observation cohort. Overall, there was no difference in frequency and severity of headache at baseline between groups; however, a history of migraines was more prevalent in the observation cohort.

At a mean of approximately 8 years following diagno-

FIG. 2. Three management modalities for VS. **A:** A 67-year-old woman with serviceable hearing was referred after being diagnosed with a 1-cm left-sided VS. **B:** Following 8 years of observation, the tumor remains unchanged, and the patient has only experienced minimal decline in hearing. **C:** A 62-year-old man presented for evaluation of a growing, 1.5-cm right-sided VS. **D:** Five years following SRS, using a marginal dose of 12 Gy, the tumor has decreased in size. **E:** A 33-year-old man with serviceable hearing was referred after being diagnosed with a 2.1-cm right-sided VS. **F:** Four months following resection, the patient has maintained preoperative hearing levels and normal facial nerve function, and imaging confirms no evidence of residual tumor.

sis, the average HDI total score for the observation cohort was 8.5 (median 0; IQR 0–12; range 0–64), compared with 4.3 (median 0; IQR 0–4; range 0–46) for nontumor control subjects. Sixty-seven (45%) of the 148 patients with VS who were observed had HDI total scores > 0 compared with 30 (29%) of the 103 nontumor controls. Univariately, the OR for the association of group (observation vs nontumor control) with HDI total scores > 0 was 2.01 (95% CI 1.18–3.43; $p = 0.010$). Thirty (20%) of the patients who were observed had HDI total scores > 14 compared with 11 (11%) of the nontumor controls, resulting in a univariate OR for the association with HDI total scores > 14 of 2.13 (95% CI 1.01–4.47; $p = 0.047$). When controlling for the 2 variables that were most strongly associated with severe HDI in this subset (HADS and presence of headaches prior to treatment), the observation cohort was still statistically significantly more likely to have severe headache disability than the nontumor control group (multivariate OR 3.01; 95% CI 1.20–7.56; $p = 0.019$).

Impact of Treatment on Headache

A comparison of clinical features among the SRS, observation, and microsurgery groups is shown in Table 3.

TABLE 1. Characteristics of 538 patients with VS

Feature*	Mean (median; IQR) or No. (%)
Baseline	
Age at survey (yrs)	63.9 (64; 55–72)
Dx to survey (yrs)	7.7 (7.7; 5.6–9.3)
Sex	
Female	303 (56)
Male	235 (44)
Location	
US	276 (51)
Norway	262 (49)
Pre-Tx	
Tumor size (n = 533)	
Intracanalicular	154 (29)
0–9 mm CPA	112 (21)
10–19 mm CPA	211 (40)
20–30 mm CPA	56 (11)
Hydrocephalus prior to Tx (n = 459)	
No	451 (98)
Yes	8 (2)
Preexisting Dx of migraine	
No	435 (81)
Yes	103 (19)
Presence of HAs prior to Tx (n = 537)	
No	219 (41)
Yes, mild	213 (40)
Yes, severe	105 (20)
Tx modality	
Observation	148 (28)
SRS	247 (46)
Microsurgery	143 (27)
Post-Tx	
HADS total score at time of survey (n = 537)	6.2 (5; 2–9)
HDI total score at time of survey	10 (2; 0–14)
Change in HAs following Tx (n = 530)	
Slightly better	76 (14)
No change	371 (70)
Somewhat worse	55 (10)
Much worse	28 (5)
Frequency of HAs over last several mos (n = 535)	308 (58)
Less than once per mo	53 (10)
Once per mo	91 (17)
Less than 4 per mo	66 (12)
Less than daily	17 (3)
Daily	
Severity of ongoing HAs (n = 522)	
Mild	334 (64)
Moderate	152 (29)
Severe	36 (7)

Dx = diagnosis; HA = headache; Tx = treatment.

* Sample sizes for features with missing data are indicated in parentheses.

Aside from tumor size, there were no baseline differences between treatment populations. At last follow-up, the microsurgery cohort had more frequent headaches; however, the perceived severity was not statistically significantly different between groups. Additionally, the percentage of respondents who reported worsening headaches after treatment was not different between groups. As outlined below, when accounting for baseline differences between groups, HDI total scores were not statistically significantly different among management modalities.

Of the 318 patients who reported having headaches prior to treatment, 109 (34%) had severe headache disability (HDI > 14) at time of survey. Within this group, 48 (44%) were treated with SRS, 25 (23%) with observation, and 36 (33%) with microsurgery. Univariately, among patients with preexisting headache, the risk for severe long-term headache disability was greatest for the microsurgery arm (OR 2.21; 95% CI 1.18–4.14; $p = 0.014$) compared with SRS (OR 1.54; 95% CI 0.87–2.73; $p = 0.14$) or the observation cohort (reference group). However, after multivariable adjustment, these differences were no longer found to be statistically significant [observation (reference), SRS (OR 1.64; 95% CI 0.86–3.14; $p = 0.13$), microsurgery (OR 1.63; 95% CI 0.78–3.40; $p = 0.19$)].

Among the 143 patients managed with microsurgery, 94 (66%) underwent retrosigmoid craniotomy, 34 (24%) translabyrinthine resection, and 15 (10%) the middle fossa approach. Overall, 45 (31%) of the patients who underwent microsurgery had severe headache disability (HDI > 14) at time of survey, with the percentage of patients within each subgroup being very similar: 5 of 15 (33%) middle fossa craniotomy, 29 of 94 (31%) retrosigmoid craniotomy, and 11 of 34 (32%) translabyrinthine resection. Univariately, the risk of long-term severe headache disability was not different between patients who underwent retrosigmoid craniotomy (reference group), translabyrinthine resection (OR 1.07; 95% CI 0.46–2.49; $p = 0.87$), and middle fossa craniotomy (OR 1.12; 95% CI 0.35–3.57; $p = 0.85$). The relatively small number of patients with severe HDI scores within the individual subgroups precluded multivariable analysis.

Within the SRS group, there were 179 patients (72%) who received a marginal dose of 12 Gy, 42 (17%) who received 13 Gy, and 26 (11%) who received 14 Gy. Univariately, the OR for the marginal dose 13 Gy versus 12 Gy to predict severe headache disability (HDI > 14) was 0.70 (95% CI 0.30–1.63; $p = 0.41$); the OR for the marginal dose 14 Gy versus 12 Gy was 0.39 (95% CI 0.11–1.36; $p = 0.14$). There were only 56 patients within the SRS cohort who had severe headache disability at time of survey, as shown in Table 3. As such, multivariable modeling could not be performed in this subset.

Predictors of Long-Term Headache Disability

Among the 538 patients with VS, the mean HDI total score was 10 (median 2; IQR 0–14; range 0–95), and there were 275 patients (51%) with HDI total scores > 0. Univariately associations of the candidate predictors for an HDI total score of > 0 are summarized in Table 4. Younger age, female sex, preexisting diagnosis of migraine, presence of headaches prior to treatment, treatment with microsurgery, and higher (poorer) HADS total score at time

TABLE 2. Comparison of features between patients with conservatively observed VS and nontumor controls

Feature	Mean (median; IQR) or No. (%)		p Value
	Controls n = 103	Observation n = 148	
Age at survey (yrs)	55.1 (56; 48–63)	67.2 (67; 61–74)	<0.001
Sex			
Female	61 (59)	88 (59)	0.97
Male	42 (41)	60 (41)	
Preexisting Dx of migraine			
No	92 (89)	112 (76)	0.006
Yes	11 (11)	36 (24)	
Preexisting Dx of HAs (n = 250)			
No	41 (40)	50 (34)	0.11
Yes, mild	51 (50)	67 (46)	
Yes, severe	11 (11)	30 (20)	
Change in HAs over last 5–10 yrs (n = 247)			
Slightly better	14 (14)	14 (10)	0.50
No change	78 (76)	117 (81)	
Somewhat worse	8 (8)	10 (7)	
Much worse	2 (2)	4 (3)	
Frequency of HAs over last several mos (n = 248)			
Less than once per mo	70 (69)	94 (64)	0.47
Once per mo	11 (11)	17 (12)	
Less than 4 per mo	7 (7)	19 (13)	
Less than daily	9 (9)	15 (10)	
Daily	4 (4)	2 (1)	
Severity of ongoing HAs (n = 242)			
Mild	77 (79)	97 (67)	0.048
Moderate	19 (19)	39 (27)	
Severe	2 (2)	8 (6)	
HADS total score	7.1 (6; 3–10)	5.9 (4; 2–8)	0.063
HDI total score >0	30 (29)	67 (45)	0.010
HDI total score >14	11 (11)	30 (20)	0.043

of survey were univariately associated with an HDI score > 0. The multivariable model developed for this end point is summarized in Table 5. After adjusting for baseline differences between treatment groups, the proportion of patients with an HDI score > 0 was not statistically significantly different between treatment modalities. Overall, the presence of headache prior to treatment was the strongest predictor of long-term headache disability.

There were 131 patients (24%) with HDI total scores > 14, indicating severe headache disability. Univariate associations of the candidate predictors for HDI total scores > 14 were similar to those seen for HDI > 0 and are summarized in Table 6. The multivariable model developed for this end point demonstrates that younger age, higher (poorer) HADS total score, preexisting diagnosis of migraine, and presence of headaches prior to treatment are associated with severe long-term headache disability (Table 7).

Within the multivariable model, there was no significant association between HDI outcome and treatment center. Specifically, the OR for the Norwegian cohort versus the US population in the multivariable model for the primary outcome of having any headache disability (HDI > 0) was 1.50 (95% CI 0.99–2.27; $p = 0.058$), while the OR in the multivariable model for the primary outcome of

severe headache disability (HDI > 14) was 1.22 (95% CI 0.73–2.02; $p = 0.45$).

Discussion

The current literature evaluating headache in patients with VS remains limited. To date, most studies have focused on pain following microsurgical resection and, in particular, retrosigmoid craniotomy.^{1,8,9,14,15,17,21,24,28,33,36–38} This narrow focus has potentially left several significant knowledge gaps. The current study examined headache outcomes among 538 patients with sporadic < 3-cm VS who were managed with microsurgery, SRS, and observation, using a validated headache disability inventory. Additionally, 103 nontumor control patients were surveyed. The primary objectives were 1) to examine the influence of disease and treatment on headache in patients with sporadic VS; and 2) to identify clinical predictors of long-term headache disability.

Prevalence of Headache in Patients With Sporadic VS

Overall, 60% of patients reported having varying severities of headache prior to treatment, and 19% recorded a positive history of migraine. Surprisingly, the net change in perceived headache symptoms at a mean of 7.7 years

TABLE 3. Univariate comparison of features among 538 patients treated with SRS, observation, or microsurgery

Feature	Tx Modality Mean (median; IQR) or No. (%)			Global Comparison	Pairwise Comparison		
	SRS n = 247	Observation n = 148	Microsurgery n = 143		SRS vs Ob	SRS vs Microsurgery	Microsurgery vs Ob
HDI total score >0 (any HA disability)	122 (49)	67 (45)	86 (60)	0.031	0.43	0.040	0.011
HDI total score >14 (severe HA disability)	56 (23)	30 (20)	45 (31)	0.059			
HADS total score (n = 537)	6.1 (4; 2–9)	5.9 (4; 2–8)	6.9 (5; 2–9)	0.57			
Tumor size (n = 533)							
Intracanalicular	35 (14)	86 (60)	33 (23)	<0.001	<0.001	0.051	<0.001
0–9 mm CPA	65 (26)	30 (21)	17 (12)				
10–19 mm CPA	128 (52)	26 (18)	57 (40)				
20–30 mm CPA	19 (8)	1 (1)	36 (25)				
Hydrocephalus prior to Tx (n = 459)							
No	224 (98)	88 (100)	139 (98)	0.51			
Yes	5 (2)	0	3 (2)				
Preexisting Dx of migraine							
No	210 (85)	112 (76)	113 (79)	0.060			
Yes	37 (15)	36 (24)	30 (21)				
Presence of HAs prior to Tx (n = 537)							
No	109 (44)	50 (34)	60 (42)	0.28			
Yes, mild	86 (35)	67 (46)	60 (42)				
Yes, severe	52 (21)	30 (20)	23 (16)				
Change in HAs following Tx (n = 530)							
Slightly better	35 (14)	14 (10)	27 (19)	0.47			
No change	174 (72)	117 (81)	80 (56)				
Somewhat worse	25 (10)	10 (7)	20 (14)				
Much worse	9 (4)	4 (3)	15 (11)				
Frequency of HAs over last several mos (n = 535)							
Less than once per mo	25 (10)	17 (12)	11 (8)	0.001	0.38	0.003	<0.001
Once per mo	33 (13)	19 (13)	39 (27)				
Less than 4 per mo	29 (12)	15 (10)	22 (15)				
Less than daily	9 (4)	2 (1)	6 (4)				
Daily							
Severity of ongoing HAs (n = 522)							
Mild	157 (66)	97 (67)	80 (57)	0.094			
Moderate	65 (27)	39 (27)	48 (34)				
Severe	15 (6)	8 (6)	13 (9)				

Ob = observation; SRS = stereotactic radiosurgery.

following treatment appeared nearly stable, with 14% noting improvement, 16% with worsening headache, and 70% having no perceivable change. At time of survey, 42% of the 538 patients reported having at least one headache per month within the preceding several months, with more than one-third of patients experiencing moderate to severe pain.

Although there are currently no studies in the VS literature focusing on longitudinal change in headache symptoms following SRS and conservative observation, surgical series have reported a frequency of baseline headache ranging from 9% to 50% and a prevalence of posttreatment headache ranging from 0% to 75%.^{17,24,28,37,38,44,45,47} The low rate of headache seen in some studies is perplexing since, within the general population, the estimated lifetime prevalence of headache is approximately 60%–80%,

with roughly 40%–60% of individuals experiencing headaches each year.^{42,43} This significant disparity probably stems from heterogeneous study methodology, varying definitions of headache, and differing lengths of follow-up. Several studies have used subjective cut-offs that only included patients with “problematic” or “bothersome” headaches. It has also been well established that the frequency of postoperative headache significantly declines with duration of follow-up—postoperative headaches are generally more severe immediately after surgery and improve significantly even by the 1st year.^{14,36} Finally, studies using prospective or cross-sectional questionnaires generally report a higher prevalence of headache and more closely approximate estimates from general population epidemiological studies, whereas retrospective chart reviews more frequently report significantly lower rates. This probably

TABLE 4. Univariate associations with any headache disability (HDI total scores > 0) in 538 patients with VS

Feature	Median or No. (%)		OR (95% CI)	p Value
	HDI Score > 0 n = 275	HDI Score = 0 n = 263		
Baseline features				
Age at survey (yrs)	61	68	0.64 (0.55–0.75)*	<0.001
Dx to survey (yrs)	7.4	7.7	1.00 (0.93–1.07)†	0.96
Sex				
Female	178 (65)	125 (48)	1.0 (reference)	
Male	97 (35)	138 (52)	0.49 (0.35–0.70)	<0.001
Pre-Tx				
Tumor size				
Intracranicular	73 (27)	81 (31)	1.0 (reference)	
0–9 mm CPA	49 (18)	63 (24)	0.86 (0.53–1.41)	0.56
10–19 mm CPA	123 (45)	88 (34)	1.55 (1.02–2.36)	0.040
20–30 mm CPA	29 (11)	27 (10)	1.19 (0.65–2.20)	0.57
Hydrocephalus				
No	239 (99)	212 (98)	1.0 (reference)	
Yes	3 (1)	5 (2)	0.53 (0.13–2.25)	0.39
Preexisting Dx of migraine				
No	194 (71)	241 (92)	1.0 (reference)	
Yes	81 (29)	22 (8)	4.57 (2.75–7.60)	<0.001
Presence of HAs prior to Tx				
No	59 (21)	160 (61)	1.0 (reference)	
Yes, mild	127 (46)	86 (33)	4.01 (2.67–6.00)	<0.001
Yes, severe	89 (32)	16 (6)	15.08 (8.19–27.76)	<0.001
Tx modality				
Observation	67 (24)	81 (31)	1.0 (reference)	
SRS	122 (44)	125 (48)	1.18 (0.78–1.78)	0.43
Microsurgery	86 (31)	57 (22)	1.82 (1.15–2.91)	0.011
Post-Tx				
HADS total score	6	3	1.12 (1.08–1.16)†	<0.001

* OR and CI represent a 10-unit increase.

† OR and CI represent a 1-unit increase.

relates to an inherent limitation of a retrospective study; if a symptom is not mentioned in the clinical note, it may be recorded as negative rather than removing the missing feature from the denominator, potentially leading to a significant underestimation of prevalence.

Do Small Sporadic VSs Cause Headache?

It is commonly held that VSs do not result in headache symptoms until they are large enough to impinge upon the fifth cranial nerve or cause obstructive hydrocephalus from fourth ventricle effacement. Though there are currently very limited data in the VS literature to validate or discredit this notion, there is convincing evidence within the general neurosurgical literature that intracranial neoplasms contribute to headache, with posterior fossa lesions being more likely than supratentorial tumors to cause head pain.^{30,44,45} Mechanisms of headache from intracranial tumors include elevated intracranial pressure from hydrocephalus or venous outflow obstruction, secondary parenchymal or subarachnoid bleed, or traction and compression of pain-sensitive dura mater, meningeal vasculature, or cranial nerves carrying sensory contributions such as the trigeminal, facial, glossopharyngeal, vagus, or upper cer-

vical rootlets.^{6,44} Suwanwela and colleagues examined the pattern of headache associated with various intracranial tumors. They identified that 15 of 17 (88%) patients with VS reported headache, which is similar to glioma (26 of 29; 90%) and more frequent than with metastatic tumors (16 of 24; 67%).⁴⁴

To investigate this issue further, we compared headache symptoms and HDI scores between 148 patients with conservatively observed tumors and 103 general population nontumor control subjects. Sixty percent of observed VSs were purely intracranial and only 1 patient had a tumor larger than 2 cm; none had hydrocephalus. While the observation group had a higher prevalence of migraine, there was no difference in the rate of preexisting headaches, change in headache symptoms over the last 5–10 years, and frequency of headaches over the last several months. However, the perceived severity of ongoing headaches and HDI scores at time of survey were statistically significantly greater in the observation group. Overall, the risk of having severe headache disability (HDI > 14 points) with a small or medium-sized untreated VS was roughly twice that of the general population. Emotional distress from diagnosis cannot account for this difference since the nontumor

TABLE 5. Multivariable model to predict any headache disability (HDI total scores > 0) in 521 patients with VS

Feature	OR (95% CI)	p Value
Age at survey (yrs)	0.67 (0.57–0.80)*	<0.001
HADS total score	1.09 (1.04–1.14)†	<0.001
Sex		
Female	1.0 (reference)	
Male	0.59 (0.39–0.88)	0.011
Presence of HAs prior to treatment		
No	1.0 (reference)	
Yes, mild	3.22 (2.09–4.96)	<0.001
Yes, severe	11.12 (5.84–21.17)	<0.001

* OR and CI represent a 10-unit increase.

† OR and CI represent a 1-unit increase.

control group actually had slightly poorer HADS results. We speculate that the most plausible explanation for increased headache disability with small VS is from dural traction within the internal auditory canal and at the porus acusticus. This is further supported by the observation that headache most commonly lateralizes to the side with the

tumor.^{24,44} Seventh nerve compression is also conceivable; however, it is very rare that patients report otalgia, such as with geniculate neuralgia or herpes zoster oticus, making this much less likely.^{10,24} Last, it is possible that tumor population selection bias also at least partially contributed to this difference. That is, in the absence of other symptoms, patients who are harboring undiagnosed VS with headache are more likely to undergo head MRI than those without headache.

Impact of Treatment on Headache

To date, there are very limited data comparing headache outcomes between treatment modalities, and no single study has specifically focused on this issue. In the current study, after accounting for baseline differences between treatment groups, HDI outcomes were not statistically significantly different among treatment modalities.

In a previous study, we found that long-term headache, determined by the PANQOL pain domain, was greater for patients receiving microsurgery compared with SRS or observation.⁵ Using the same measure, Robinett et al. reported a similar finding at 0–5 years of follow up; however, no statistically significant difference in pain was iden-

TABLE 6. Univariate associations with severe headache disability (HDI total scores > 14) in 538 patients with VS

Feature	Median or No. (%)		OR (95% CI)	p Value
	HDI Score > 14 n = 131	HDI Score ≤ 14 n = 407		
Baseline features				
Age at survey (yrs)	59	66	0.65 (0.55–0.77)*	<0.001
Dx to survey (yrs)	7.7	7.6	1.02 (0.94–1.10)†	0.71
Sex				
Female	89 (68)	214 (53)	1.0 (reference)	
Male	42 (32)	193 (47)	0.52 (0.35–0.79)	0.002
Pre-Tx				
Tumor size				
Intracanalicular	38 (29)	116 (29)	1.0 (reference)	
0–9 mm CPA	19 (15)	93 (23)	0.62 (0.34–1.15)	0.13
10–19 mm CPA	56 (43)	155 (38)	1.10 (0.68–1.78)	0.69
20–30 mm CPA	17 (13)	39 (10)	1.33 (0.68–2.62)	0.41
Hydrocephalus				
No	113 (97)	338 (99)	1.0 (reference)	
Yes	3 (3)	5 (1)	1.80 (0.42–7.63)	0.43
Preexisting Dx of migraine				
No	79 (60)	356 (87)	1.0 (reference)	
Yes	52 (40)	51 (13)	4.60 (2.91–7.26)	<0.001
Presence of HAs prior to Tx				
No	22 (17)	197 (49)	1.0 (reference)	
Yes, mild	46 (35)	167 (41)	2.47 (1.43–4.27)	0.001
Yes, severe	63 (48)	42 (10)	13.43 (7.45–24.19)	<0.001
Tx modality				
Observation	30 (23)	118 (29)	1.0 (reference)	
SRS	56 (43)	191 (47)	1.15 (0.70–1.90)	0.58
Microsurgery	45 (34)	98 (24)	1.81 (1.06–3.08)	0.030
Post-Tx				
HADS total score	8	4	1.14 (1.10–1.19)†	<0.001

* OR and CI represent a 10-unit increase.

† OR and CI represent a 1-unit increase.

tified between groups after 5 years.³⁴ Other studies have similarly demonstrated that differences in pain are greatest early after treatment; however, this disparity significantly declines within several years.²⁹

A number of studies evaluating pain after microsurgery have demonstrated that retrosigmoid craniotomy has a higher early prevalence of headache compared with translabyrinthine and middle fossa resection.^{19,28,36,37,45} There are many explanations for this finding. Several studies have demonstrated a reduction in postoperative headache after using cranioplasty, suggesting that adhesions between nuchal muscles and posterior fossa dura may cause pain.^{15,21,33} Jackson et al. compared the rate of postoperative headache following retrosigmoid craniotomy for vestibular nerve section and VS surgery and found that headache following tumor resection was substantially greater, suggesting that headache resulted from disseminated intracranial bone dust from drilling the porus of the internal auditory canal at the time of resection, causing aseptic meningitis.^{13,17} Ducic et al. reported significant improvement in headache following occipital nerve resection in 6 of 7 patients, implicating nerve entrapment or neuroma formation.⁹ Levo reported a marked improvement or resolution of pain in 9 subjects using sumatriptan, leading to the conclusion that some postoperative headache may be mediated by the trigeminal nerve.²³

In the current study, both participating centers used very similar techniques for the retrosigmoid approach. A vertically oriented retroauricular curvilinear incision was made, and a craniotomy was performed following a single bur hole placed just below the transverse-sigmoid sinus junction, preserving a bone flap. Following tumor resection, bone dust was meticulously evacuated from the cistern, the dura was closed primarily, and Gelfoam was placed over the dura. The bone flap was replaced by securing it with standard titanium microplates and screws. Polymethylmethacrylate or other methods of cranioplasty were not performed.

Several studies have demonstrated that the severity of headache following retrosigmoid craniotomy decreases with time.^{14,17,36–38} Ruckenstein et al. examined 52 patients who underwent translabyrinthine and retrosigmoid craniotomy for VS and reported a higher prevalence of headache at 1 and 6 months with retrosigmoid surgery; however, at 1 year, there was no difference between groups.³⁶ The comparison between middle cranial fossa and other approaches is not as well studied. A systematic review found that retrosigmoid craniotomy had the highest prevalence of headache, translabyrinthine resection had the lowest, and middle cranial fossa had an intermediate rank.¹ Although translabyrinthine resection and middle fossa craniotomy limit intracranial bone dust from extradural drilling, division of the temporalis muscle with middle cranial fossa may explain the higher rate of pain. This theory is corroborated by the high frequency of myofascial pain involving the temporalis muscle experienced by patients undergoing open cerebral aneurysm repair.³⁵

Clinical Predictors of Long-Term Headache Disability

In the current study, we identified several predictors of long-term headache disability. In a multivariable model, younger age, higher (poorer) HADS total score, female

TABLE 7. Multivariable model to predict severe headache disability (HDI total scores > 14) in 538 patients with VS

Feature	OR (95% CI)	p Value
Age at survey (yrs)	0.69 (0.57–0.84)*	<0.001
HADS total score	1.15 (1.10–1.20)†	<0.001
Preexisting Dx of migraine		
No	1.0 (reference)	
Yes	1.82 (1.01–3.29)	0.046
Presence of HAs prior to Tx		
No	1.0 (reference)	
Yes, mild	1.80 (0.99–3.30)	0.056
Yes, severe	8.84 (4.36–17.93)	<0.001

* OR and CI represent a 10-unit increase.

† OR and CI represent a 1-unit increase.

sex, and preexisting diagnosis of headaches were associated with HDI scores > 0. When specifically analyzing predictors of severe headache disability (HDI > 14), younger age, HADS total score, preexisting diagnosis of migraine, and presence of headaches prior to treatment were statistically significant. When considering all factors, a preexisting diagnosis of headache was the strongest predictor of poor HDI total score. Ryzenman et al. analyzed postoperative headache results from the 1998 Acoustic Neuroma Association survey including 1657 surgically treated patients who were surveyed a mean of 8 years after treatment.³⁷ Similar to the current study, pretreatment headache, female sex, and younger age were identified to be associated with poorer postoperative headache outcomes. Levo and colleagues evaluated 251 patients who underwent resection of VS and found that after a mean of 8.9 years, persistent headache was associated with the retrosigmoid approach, small tumor size, gait problems, and preoperative headache.²⁴

It is notable that younger age and female sex are also strongly associated with headache within the general population.^{42,43} Additionally, it has been shown that anxiety and depression heavily influence headache symptoms.^{20,25,33,46} Therefore, the factors that most significantly influence long-term headache in VS are not specific to the diagnosis, but rather are the same predictors for headache in the general population. The importance of asking about baseline headaches cannot be overemphasized. Unfortunately, in the clinical setting, headaches after treatment are frequently blamed on the treatment itself, even in the presence of a preexisting headache syndrome. The fact that the long-term prevalence of headache in patients with VS closely matches that in the general population, and that the number one predictor of posttreatment headache is the existence of pretreatment headache, suggest that long-term headache may actually have more to do with the patient than with the diagnosis of VS or its treatment. Based on this current analysis, we no longer specifically counsel patients with a headache history that they should strongly avoid microsurgery as a treatment option for their VS.

Headache Classification and Treatment

Whereas the current study did not attempt to classify headache subtypes or determine response to therapy, several previous studies have examined symptom profiles to

categorize headache types according to the International Classification of Headache Disorders, Second Edition (ICHD-II) diagnostic criteria.^{13,33,39} Rimaaja and colleagues characterized pre- and postoperative headache in 61 and 122 patients, respectively.³³ Before surgery, 77% of patients had migraine with or without aura, 15% had tension-type headache, and the remaining patients were unclassified. Following surgery, 89 of the 122 patients with headache experienced postoperative headache only, whereas 39 reported both pre- and postoperative headache. New postoperative headache met ICHD-II diagnostic criteria for tension-type headache in 4 cases, and for migraine with or without aura in 15, with most remaining patients fitting a specific subgroup of postcraniotomy headache. Schankin et al. found that among 30 patients with severe (≥ 6 of 10 pain) postoperative headache persisting beyond 6 months, 47% had tension-type headache, 17% occipital neuralgia, 17% trigeminal neuralgia, 10% nervus intermedius neuralgia, and 10% cervicogenic headache.³⁹

Levo et al. reported that approximately one-quarter of patients with postoperative headache did not require pain medications, more than three-quarters had symptomatic improvement or resolution of pain with antiinflammatory agents, and only 3% received no help from medication.²⁴ Similarly, Rimaaja and colleagues found that simple analgesics (nonsteroidal antiinflammatories, coxibs, or acetaminophen) provided partial or complete pain relief in 79% of patients with postoperative headache, whereas antiepileptic agents (gabapentin and carbamazepine), tricyclic antidepressants, and muscle relaxants were used much less frequently.³³ Finally, Hanson et al. reported their experience managing pain after suboccipital VS resection, finding that approximately 13% of patients did not respond to simple analgesic therapy.¹³ Within the small group of patients with refractory symptoms, divalproex sodium and verapamil provided significant relief in all cases.

We wish to acknowledge several strengths and limitations of the current study. To date, the majority of publications investigating headache in VS have examined relatively early postoperative symptoms in a limited sample size using self-devised questionnaires. To our knowledge, no study has characterized headache in conservatively managed patients or in those receiving SRS. Furthermore, none have used a validated headache disability questionnaire to assess the impact of headache on daily life. In the current study, we compared long-term headache outcomes among patients managed with observation, SRS, and microsurgery. Additionally, a nontumor control group was surveyed to determine the impact of diagnosis on headache.

The primary limitation of the current study is the lack of baseline or longitudinal data to evaluate change in headache disability and symptomatology over time. Patients were required to recollect symptoms that were present many years earlier, introducing the risk of recall bias. Additionally, these data provide a cross-sectional snapshot of headache disability at approximately 8 years following treatment and do not describe disability in the early period after treatment, which may be different, particularly for the surgical cohort. Furthermore, despite using a validated inventory, questionnaire responses assessing handicap are subjective—2 patients with similar headache severity and

frequency may give significantly different responses. Finally, headache subtype and response to therapy were not characterized, given the retrospective nature of the study.

Conclusions

At a mean of approximately 8 years following treatment, 42% of VS patients were experiencing at least monthly headaches. When analyzing all patients, we found no difference in long-term HDI scores among treatment groups. Multivariable regression revealed that patient-related features such as age, sex, pretreatment headache, and emotional distress are the strongest predictors of long-term headache disability, whereas disease-associated features including tumor size and treatment modality have much less influence.

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