THE ASSOCIATION OF VESTIBULAR SCHWANNOMAS AND PITUITARY ADENOMAS: A POPULATION BASED STUDY

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INTRODUCTION

Vestibular schwannomas (VS) are rare benign slow growing tumors that arise from the vestibular portion of the eighth cranial nerve. Overall they represent only 8% of all intracranial tumors and demonstrate an incidence of approximately 1-2 per 100,000 population.[1] Pituitary adenomas (PA) represent a heterogeneous group of extra-axial neoplasms that collectively comprise approximately 13% of all intracranial tumors with a prevalence of approximately 3 per 100,000.[2]

Over the years the authors have evaluated a number of patients with sporadic unilateral VS who were also diagnosed with PAs. There are only three possible explanations for concomitant VS and PA development including chance occurrence, environmental influence, or genetic predisposition. Given the rare incidence of these tumors, we speculated that the frequency of which we encountered this event was far greater than chance occurrence. Currently there are no known epidemiological or well-characterized genetic associations between VS and PA. Additionally in a large percentage of patients, the precise cause for development of either tumor remains unknown.[3-6] The objective of the current study is to characterize an epidemiological association between VS and PA using a large national tumor registry database.

METHODS

SEER Database Analysis

The Surveillance, Epidemiology and End Results (SEER) database was searched and cases were selected using the International Classification of Diseases for Oncology (ICD-O-3) code for benign schwannoma (9560/0) with associated topography code (C72.4) for auditory and vestibular nerve and ICD-O-3 codes for benign pituitary adenoma (8140/0, Adenoma NOS; 8202/0, Microcystic adenoma; 8260/0, Papillary adenoma NOS; 8270/0, Chromophobe adenoma; 8271/0, Prolactinoma; 8272/0, Pituitary adenoma NOS; 8280/0, Acidophil adenoma; 8281/0, Mixed acidophil-basophil adenoma; 8290/0, Oxyphilic adenoma; 8300/0, Basophil adenoma) with associated topographical code (C75.1) for pituitary gland. Patients with alternate coding were excluded. Tumor size was categorized as 0-1 cm, 1-2 cm, 2-3 cm, 3-4 cm, over 4 cm, and missing. For the purpose of classifying pituitary tumors, a PA smaller than 1cm was classified as a microadenoma, and those 1cm or larger were labeled macroadenoma.

The annual population denominators for the registries (a surrogate for person-years of observation) were taken from SEER-Stat for the calendar years of our specific study, and the observed incidence rates were calculated for VS-only, for PA-only, and for the co-occurrence of VS and PA. Incidence rates are calculated by dividing the number of observed cases of VS and PA by the total number of person-years under observation. Based on the observed incidence rates of VS-only cases and PA-only cases, the expected incidence rate for coexisting VS and PA under the assumption of independence can be calculated as the product of the two separate incidence rates.[9] A 95% confidence interval (95% CI) was estimated assuming the observed number of events follows a Poisson distribution and the expected number of events is fixed. Finally, the observed-to-expected ratio (O/E) is calculated by dividing the observed number of cases with coexisting VS and PA by the expected number.[9] This ratio quantifies how frequent these two conditions actually occurred together compared to chance occurrence. For example, an O/E of 10 means these two conditions co-occurred 10 times more frequently than expected assuming independence.

RESULTS

SEER Database Analysis

Between 2004 and 2012 a total of 9,888 patients with VS, from the SEER registry populations totaling 822.9 million person-years, were reported in the SEER database. The mean age at diagnosis was 54.9 years (SD 14.8) and there were slightly more women than men (52.1% vs. 47.9%). The most commonly reported ethnicity was Non-Hispanic White, followed by Hispanic. The observed incidence during this time interval was 1.2 VS per 100,000 person-years (**Table 1**).

Over this same time period, a total of 26,577 PAs were reported in the SEER database. The mean age at diagnosis was 50.1 years (SD 18.4) and there were 10.6% more women than men (55.3% vs. 44.7%). Similar to the VS population, the most commonly reported ethnicity was Non-Hispanic White, followed by Hispanic. The observed incidence during this time interval was 3.2 PA per 100,000 person-years, approximately 3 times the incidence of VS (**Table 3**).

Between 2004 and 2012, 31 patients (95% CI 21.1-44.0) with concomitant VS and PA were reported, providing an observed incidence rate of 3.8×10^{-3} (95% CI 2.6×10^{-3} - 5.4×10^{-3}) cases per 100,000 person-years. The expected rate of having both conditions, determined by calculating the product of the two separate incidence rates, was 3.88×10^{-5} cases per 100,000 person-years. From these data, the calculated O/E ratio was 97.1 (95% CI 66.0-138) (**Table 3**). That is, there were 97-fold more cases with both conditions than one would expect under independence of these two conditions. Of the 31 patients with both tumor types, 15 were diagnosed synchronously, whereas 16 cases were diagnosed sequentially. The diagnosis of VS then PA was made in 6 cases and PA followed by VS in 10 cases. The mean time delay between diagnosis of the first and second tumor was 11.3 months (range 0-88 months).

On average, every 319 patients with VS also harbored a PA. The average age of this cohort was 59.9 years (SD 13.4); 4.8 years greater than the VS-only group (P=0.07) and 9.8 years greater than the PA only group (P=0.002). In contrast to the two single-tumor populations, patients with VS and PA were more frequently men (64.5% vs. 47.9% in VS group, P=0.06 and 44.7% in PA group, P=0.03). There were no statistically significant differences between groups with regard to tumor size or reported ethnicity. Within the subgroup of 31 patients, 6 had a third tumor type reported, only 1 of which was intracranial. There was no difference in the reported distribution of histological subtype between all PAs and the 31 with co-existing VS (**Table 2**).

Table 3. Observed and expected incidence calculations for vestibular schwannoma and pituitary adenomas

Year	# VS	# PA	# PA+VS	Total SEER Population	Observed VS Incidence*	Observed PA Incidence*	Observed VS+PA Incidence*	Expected VS+PA Incidence*	Observed to expected rate ratio
2004	1,060	2,323	0	88,254,554	1.201071	2.632159	0	0.00003161	0
2005	992	2,512	1	88,929,243	1.115494	2.847176	0.001124	0.00003151	35.69
2006	1,119	2,674	3	89,688,379	1.247653	2.981434	0.003345	0.00003720	89.92
2007	1,113	2,819	2	90,542,359	1.229259	3.113460	0.002209	0.00003827	57.72
2008	1,126	2,926	7	91,469,224	1.231015	3.198890	0.007653	0.00003938	194.34
2009	1,186	3,215	4	92,325,435	1.284586	3.482247	0.004333	0.00004473	96.85
2010	1,087	3,303	4	93,158,638	1.166827	3.545565	0.004294	0.00004137	103.79
2011	1,041	3,438	6	93,886,873	1.108781	3.661854	0.006391	0.00004060	157.40
2012	1,164	3,367	4	94,620,901	1.230172	3.558410	0.004227	0.00004377	96.57
All years	9,888	26,577	31	822,875,606	1.201640	3.229771	0.003767	0.00003881	97.07

* Incidence per 100,000 person years.

Table 1. Epidemiologic features of 9,857 patients with vestibular schwannoma, 26,546 with pituitary tumors, and 31 with concomitant vestibular schwannoma and pituitary adenomas

Feature	VS Only (N=9,857)	PA Only (N=26,546)	Both Tumors (N=31) VS size	Both Tumors (N=31) PA Size	VS+PA vs. VS Only (P-Value)*	VS+PA vs. PA Only (P-Value)*
Tumor Size					0.6281	0.7381
Missing	2303 (23.4%)	6512 (24.5%)	4 (12.9%)	7 (22.6%)		
0-1 cm	1773 (18.0%)	5498 (20.7%)	8 (25.8%)	6 (19.4%)		
1-2 cm	2844 (28.9%)	5503 (20.7%)	11 (35.5%)	8 (25.8%)		
2-3 cm	1544 (15.7%)	5088 (19.2%)	5 (16.1%)	6 (19.4%)		
3-4 cm	810 (8.2%)	2410 (9.1%)	2 (6.5%)	4 (12.9%)		
Over 4 cm	583 (5.9%)	1535 (5.8%)	1 (3.2%)	0 (0.0%)		
Year					0.1820	0.2971
2004	1060 (10.8%)	2322 (8.7%)	0 (0.0%)	1 (3.2%)		
2005	991 (10.1%)	2512 (9.5%)	1 (3.2%)	0 (0.0%)		
2006	1116 (11.3%)	2671 (10.1%)	3 (9.7%)	3 (9.7%)		
2007	1111 (11.3%)	2818 (10.6%)	2 (6.5%)	1 (3.2%)		
2008	1119 (11.4%)	2920 (11.0%)	7 (22.6%)	6 (19.4%)		
2009	1182 (12.0%)	3209 (12.1%)	4 (12.9%)	6 (19.4%)		
2010	1083 (11.0%)	3298 (12.4%)	4 (12.9%)	5 (16.1%)		
2011	1035 (10.5%)	3434 (12.9%)	6 (19.4%)	4 (12.9%)		
2012	1160 (11.8%)	3362 (12.7%)	4 (12.9%)	5 (16.1%)		
Age					0.0642	0.0018
Mean (SD)	54.9 (14.8)	50.1 (18.4)	59.9 (13.4)	60.0 (13.6)		
Age Group					0.3109	0.0208
Under 50	3552 (36.0%)	13407 (50.5%)	8 (25.8%)	8 (25.8%)		
Age 50-59	2497 (25.3%)	4461 (16.8%)	7 (22.6%)	7 (22.6%)		
Over 60	16 (51.6%)	8678 (32.7%)	3808 (38.6%)	16 (51.6%)		
Gender					0.0727	0.0301
Male	4723 (47.9%)	11866 (44.7%)	20 (64.5%)	20 (64.5%)		
Female	5134 (52.1%)	14680 (55.3%)	11 (35.5%)	11 (35.5%)		
Ethnicity					0.2304	0.2872
Non-Hispanic white	7345 (74.5%)	14525 (54.75)	19 (61.3%)	19 (61.3%)		
Hispanic	821 (8.3%)	4395 (16.6%)	6 (19.4%)	6 (19.4%)		
Non-Hispanic black	403 (4.1%)	4701 (17.7%)	1 (3.2%)	1 (3.2%)		
Non-Hispanic Asian or Pacific Islander	855 (8.7%)	1984 (7.5%)	3 (9.7%)	3 (9.7%)		
Other or Unknown	433 (4.4%)	941 (3.5%)	2 (6.5%)	2 (6.5%)		

Table 2. Histological subtypes of pituitary adenomas reported overall and within the select group of patients having co-existing vestibular schwannoma and pituitary adenoma

ICD-0-3 Code: Pituitary Adenoma Subtype	All Patients with PA	Patients with VS+PA
8140/0: Adenoma, NOS	2193 (8.3%)	1 (3.2%)
8202/0: Microcystic adenoma	3 (0.0%)	0 (0.0%)
8260/0: Papillary adenoma, NOS	9 (0.0%)	0 (0.0%)
8270/0: Chromophobe adenoma	242 (0.9%)	1 (3.2%)
8271/0: Prolactinoma	957 (3.6%)	2 (6.5%)
8272/0: Pituitary adenoma, NOS	23,117 (87.0%)	27 (87.1%)
8280/0: Acidophil adenoma	33 (0.1%)	0 (0.0%)
8281/0: Mixed acidophil-basophil adenoma	1 (0.0%)	0 (0.0%)
8290/0: Oxyphilic adenoma	16 (0.1%)	0 (0.0%)
8300/0: Basophil adenoma	6 (0.0%)	0 (0.0%)

CONCLUSIONS

- Using a large population based tumor registry, the current study demonstrates that the observed rate of co-incident VS and PA is greater than what is expected by chance alone.
- These data suggest that a common environmental or genetic predisposition exists for VS and PA development.
- Further study of this population may help elucidate the cause of tumorigenesis in a subset of patients with seemingly sporadic tumors.

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