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Neurofibromatosis 2 Invasion of the Internal Auditory Canal Wall: Clinical Significance

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Introduction

Neurofibromatosis type 2 (NF2) is a tumor predisposition syndrome caused by germline or early embryonic heterozygous mutation of the *NF2* gene on chromosome 22q. The incidence is approximately one in 25,000 live births, and the disease demonstrates nearly 100% penetrance by the age of 60 years.¹ Manifestations of NF2 include central nervous system tumors (schwannomas, meningiomas, ependymomas, and rarely astrocytomas), ophthalmological lesions (cataracts, epiretinal membranes, and retinal hamartomas), and cutaneous lesions (skin tumors).¹ NF2 patients experience devastating consequences and a decreased life expectancy as a result of tumor growth when the disease exhibits a severe phenotype, classically termed “Wishart” type NF2, that presents at an early age, with rapid tumor progression, and accompanied by various additional schwannomas, meningiomas, and ependymomas. This is in contrast to the milder NF2 phenotype, classically termed the “Gardner” type, that presents later in life with only bilateral VS that grow more slowly, or occasionally not at all, as a manifestation of the NF2 disease.²

The propensity for NF2-related vestibular nerve schwannomas (VS) for infiltrating the auditory nerve rather than impinging against the wall of the internal auditory canal (IAC) was described in 1972 and 1980.^{3,4} These findings explained why these tumors could reach considerable size before hearing was affected and why removal of even small tumors could sacrifice the hearing due to the varying location of the auditory nerves within the tumor. The tendency of these tumors to invade the cochlea and vestibule has also been described.^{5,6} The presence of tumor within the inner ear, which can be determined with magnetic resonance imaging (MRI), compounds the difficulty with treatment of these tumors.⁷ NF2-related tumors may also invade the marrow spaces and pneumatic cells and cause destruction of the IAC bone.⁸ This invasive tendency is characteristic of the severe phenotype of NF2.

Although these terms are rarely referred to presently, we have used them in this study for simplification and to describe the data.

In this study, we describe and illustrate cases in which the severe Wishart type of NF2-related VS invaded the bone of the IAC rather than simply expanding it, as occurs with

sporadic and with the milder Gardner type NF2-related tumors. These invasions appeared as buds off of the main tumor mass and were often overlooked at the time of surgery.

Methods

From our database containing clinical and histopathological information on 1,698 temporal bones, 56 hTBs were identified from patients with VS. Of these, 37 qualified as having tumor involving the IAC. Twenty-four of these were from individuals with bilateral tumors (12 patients), defining a diagnosis of NF2, and the remaining thirteen were sporadic VS. These bones were acquired through our temporal bone pledge program that was established in 1950 and now has a St. Vincent Medical Center IRB #06-030. The bones are removed intracranially by trained technicians and fixed in buffered formalin for two weeks. They are then decalcified in ethylenediaminetetracetic acid until shown by X-ray to be free of calcium. The specimens are then embedded in celloidin and cut into 20-micron sections that are put onto numbered sheets. Every tenth section is stained with hematoxylin and eosin and placed on a glass slide; the other nine sections of each ten is saved for use in immunohistochemistry or 3D reconstruction. The microscopic findings are added to the database containing the clinical record.

Previous evaluation had indicated that the IAC wall was eroded in many of the NF2 cases but only enlarged in the cases of sporadic unilateral VS. For this study, a more detailed evaluation of the walls of the IAC was done, and illustrative images were obtained.

In addition, we investigated the phenotype in each patient from the clinical chart, defining those with aggressive disease (age ≤ 25 at diagnosis and multiple other intracranial tumors, including other cranial nerve schwannomas and meningiomas) as the severe phenotype (classically termed “Wishart” type). Those patients with a more benign clinical course, including late age of symptom onset or diagnosis (age > 25) and with the presence of only bilateral VS, classifying them as NF2 (i.e., no other cranial tumors identified on magnetic resonance imaging), were defined as the mild phenotype (classically termed “Gardner” type).

Hearing was compared for patients using the last audiogram in the chart prior to tumor resection, when available, or the last audiogram prior to death, if no tumor resection was done. Air conduction thresholds at 250, 500, 1000, 2000, 3000, 4000, and 6000 Hertz (Hz) were recorded, and the pure tone average (PTA) was calculated by averaging thresholds at 500, 1000, 2000, and 3000 Hz, per AAO-HNS criteria.⁹ When the 3000 Hz threshold was not recorded, thresholds at 2000 and 4000 Hz were averaged, and this value was substituted for the threshold at 3000 Hz. AAO-HNS criteria for speech discrimination score (SDS) using NU6 word lists (25 words) was recorded. Additionally, clinical charts were reviewed for the number and timing of tumor-related surgeries with respect to hearing and tumor recurrence. Tumors were deemed recurrent when a repeat resection was performed on the ipsilateral side after a “near-total” or “complete” resection was dictated in the operative report and/or there was radiographic evidence of significant tumor recurrence or growth after resection noted in the chart. Also, date and cause of death with respect to the tumor resection were recorded in a Microsoft Excel spreadsheet for statistical analyses. Analyses

were made using t-test when assumption of equal variances was met and nonparametric Mann-Whitney when not met within groups and between groups, with and without evidence of tumor invasion of the IAC for the following: NF2 status, hearing level, SDS, and tumor recurrence.

Results

Infiltration of the bone surrounding the IAC was apparent on at least one side in all of the cases with 'Wishart' type of NF2 (n=11) but none of the 'Gardner' type (n=1) or sporadic VS (n=13)(Table 1). There was no predilection for involvement of a particular part of the IAC; the invasions could occur medially or laterally and at varying points about the circumference of the canal. The invasions appeared as semi-pedunculated tumor mass incursions into the bone surrounding the IAC from the schwannoma within the canal lumen.

This invasion was in contrast to the expansile enlargement of the tumors seen in the cases of sporadic VS (Figs. 1 and 2). Occasionally, there was evidence of new bone formation, possibly an attempt at healing, as a result of an inflammatory response or devascularization after surgery, between the tumor and the bone (Fig. 1B). The infiltrative tendency of NF2 'Wishart'-associated tumors is illustrated in Figure 2A, where the tumor cells can be seen invading fibrosis filling the anterior basal segment of the cochlea (Fig. 2). In contrast, sporadic VS were observed to expand into the modiolus and IAC, rather than infiltrating the surrounding tissue or invading and eroding bone (Fig. 2B). IAC invasion was significantly associated with the severe 'Wishart' NF2 phenotype, where it was present in 88.9% (16 of 18 evaluable cases) of hTBs ($p<0.001$) compared with none (0/13) of the sporadic cases and was not present on either side in the mild 'Gardner' NF2 phenotype (0/2) (Table 2). However, there was only a single case of the milder 'Gardner' NF2 phenotype; therefore, no statistical correlations were possible. Among the 'Wishart' cases, 83% of those with invasion in one ear had invasion in the other. There were no cases of the severe 'Wishart' NF2 phenotype that did have at least one IAC demonstrating tumor invasion into the bone histologically.

There were no statistically significant differences between the two groups in terms of patient gender. Sidedness of the tumor (right vs. left ear) for the sporadic VS group trended towards right ear involvement (76.9%) versus left (23.1%) but was not significant. Patient age at death was significantly lower for the 'Wishart' NF2 group (avg. 34; range: 17-53 years) than for the sporadic VS group (avg. 81; range: 61-94 years)(Table 2). Also, tumor size differed significantly between the 'Wishart' group (avg. 3.8 cm; range 1-9 cm) and sporadic VS group (avg. 1.7 cm; range 0.2-3.5 cm)(Table 2). These latter two distinctions are expected variances based on the natural history of NF2 and sporadic VS.^{1, 2, 4}

The 'Wishart'-associated tumor "buds" invading the IAC were evident radiographically in two cases, where magnetic resonance imaging data (MRI) was available (Fig. 3).

Ten of the twelve NF2 patients had undergone surgery for removal of at least one of their tumors (Eighteen of the 24 hTBs). Recurrence was only recorded in four cases (22%); all in patients who demonstrated the severe 'Wishart' NF2 phenotype. Two of the recurrent

tumors had evidence of invasion (#211, right, & #763, right). One of the recurrent cases subsequently underwent a complete transotic resection such that no IAC bone was apparent in the specimen (#815, right), precluding examination for IAC bone invasion. The remaining recurrent tumor case had undergone initial surgery at another institution, and the operative report was not available; however, there was no evidence of IAC bone invasion on this side (#255, right). None of the sporadic tumors in this sample recurred after resection (0/5). Overall, residual tumor within the IAC was present histologically in 15 of the 25 tumors (65%) that were resected, including twelve of the 18 NF2 cases (67%) and three of the five sporadic cases (60%)(Table 2).

There were significant differences in hearing thresholds between ears with IAC invasion versus no invasion for frequencies up through 2,000 Hz, and borderline significance for 3,000 Hz and pure tone averages (PTA). Speech discrimination score (SDS) also differed significantly ($p=0.037$) between these two groups, with worse SDS when IAC invasion was present (mean SDS: 30%, SD 39.2) versus absent (mean SDS: 63%, SD 39.7). Hearing thresholds at 250, 500, 100, and 2000 Hz were significantly greater in the group with IAC invasion (“buds”) versus no invasion (“no buds”) but did not achieve significance for differences at 3000, 4000, and 6000 Hz (Table 3). The differences in PTA approached significance ($p=0.054$), with IAC invasion demonstrating greater PTA elevation at a mean of 86 dB (“buds”) versus 57 dB without invasion (“no buds”)(Table 3). There were only two ‘Wishart’ NF2 cases without invasion (“no buds”) and evaluable hearing, which precluded analysis within the ‘Wishart’ NF2 group for an independent hearing comparison between cases with invasion and no invasion; however, the two without invasion appeared to have better hearing than those with invasion (Table 3).

Discussion

We have described, for the first time, to our knowledge, the frequent finding of bone invasion along the IAC wall with NF2-associated tumors in patients demonstrating the severe phenotype described by Wishart in 1822.¹⁰ This finding was not present in association with sporadic VS or with the milder NF2 phenotype, historically termed ‘Gardner’ after its description in 1930.¹¹ However, it was present in the majority (89%) of hTBs from patients with the severe ‘Wishart’ NF2 phenotype (Tables 1 & 2).

We investigated the clinical history for tumor recurrence after resection in order to examine whether tumor invasion of the IAC correlated with clinical recurrence. No relationship was seen statistically. However, there were few cases with recurrences ($n=4$, 16% overall; 18% of NF2-associated tumors) when compared with non-recurrence, and all of the recurrences occurred in the severe NF2 phenotype (‘Wishart’) patients. It should be noted that the life span after tumor resection for the NF2 group was short while the sporadic group survived for many years after VS resection with the potential for recurrence; yet no clinical recurrences were seen in this group and four were seen during the limited lifespan of the twelve NF2 patients. This speaks to the notorious greater recurrence rate associated with NF2-associated tumors.¹² Residual tumor within the IAC was noted histologically in the majority of cases (65%), with no differences between NF2 (67%) and sporadic tumors (60%)(Table 2). Most were dictated as near-total resection in the operative report so this

histological finding of residual tumor is not surprising, and there was no association between residual tumor and recurrence.

However, many of these 'Wishart' patients died either in the post-operative period or died from complications of NF2 or surgery within a few years of surgery (7/11 or 64% of patients). We must consider that the majority of these patients were treated during the early days of neurotologic surgery when mortality rates were high for cerebellopontine angle (CPA) tumor resection. Six of the eleven (55%) 'Wishart' patients died from aspiration pneumonia, likely related to lower cranial nerve palsy; one from obstructive hydrocephalus and brainstem compression, and three died within the immediate post-operative period from surgical complications. Because of the inherent lack of long-term tumor follow-up in the majority of the NF2 patients, it is not possible to establish an accurate clinical recurrence rate. In contrast, the sporadic patients survived for long-term follow-up, and there were no recurrences in this group.

We have shown that, at least in some cases, the IAC wall invasion may be detected on MRI (Fig. 3). However, since the collection of hTBs from which these cases were selected dates back to the early 1960's, MRI data was not available for most cases; rather pantopaque myelography imaging confirmed the presence of bilateral IAC/CPA tumors prior to surgery. Further investigations with current and future patients will need to be done in order to ascertain whether invasion of IAC bone can be reliably detected radiographically.

We investigated the clinical history for hearing results in order to determine whether tumor invasiveness correlated with hearing loss. There was a significant association with poorer SDS in ears with IAC invasive tumors (Table 3). Additionally, elevated thresholds at pure tones of 250, 500, 1000, and 2000 Hz were associated with invasive tumors. Elevation of the PTA approached significance for a relationship with IAC invasiveness but was not statistically significant (Table 3). The hearing effects of these invasive tumors is not likely to be directly related to the invasion of the IAC wall; rather, it suggests that these aggressive tumors are secreting factors, such as proteolytic or osteolytic enzymes, that may also affect hearing. This theory is supported by VS studies relating hearing to secreted factors such as the finding that sporadic VS secretion of fibroblast growth factor 2 (FGF2) is associated with better hearing.¹³ Additionally, genetic factors within sporadic VS, specifically, increased expression of *CEA*, *PEX5L*, *RAD54B*, *PSMAL*, have been linked to hearing loss, irrespective of tumor size.¹⁴ Of these, *CEA* has also been associated with increased invasiveness in breast¹⁵ and lung cancers.¹⁶ The significance of *PSMAL* is unknown, but the gene is 98% homologous to prostate specific membrane antigen,¹⁷ which has been associated with invasiveness and is highly expressed in primary gliomas and breast cancer brain metastases.¹⁸

The invasive nature of NF2-associated tumors may partially explain their higher recurrence rate after tumor resection since a complete resection may not be attained.¹² Surgeons managing NF2-related VS should be aware of the small infiltrations of the wall of the IAC when removing these tumors in order to minimize recurrence. Endoscopy of the IAC after tumor removal might assist the surgeon in detecting tumor remnants that have invaded the bone and facilitate complete tumor resection, reducing recurrence rates.^{19, 20}

Limitations of this study include the paucity of the milder ‘Gardner’ NF2 phenotype patients within our hTB collection. Additionally, many of these patients, especially those with NF2, were evaluated and treated during the infancy of microscopic neurotologic surgery and neuroradiology such that MRI data is not available to assess the IAC invasiveness radiographically for the majority of this group, and many of these patients died soon after surgery from complications of the disease or the surgical resection, which limited the data on long-term tumor recurrence rates among the NF2 group. Further research on this phenomenon in temporal bone laboratory setting will be necessary in order to determine whether IAC invasiveness is associated with tumor recurrence in NF2.

Conclusion

We have shown evidence for invasion of the bone of the IAC wall with tumors in association with the severe NF2 (‘Wishart’) phenotype. Our investigation of hTBs demonstrates that such invasions of bone were not present for sporadic VS. Additionally, the invasive tumors were associated with poorer hearing, particularly word understanding, in the ipsilateral ear, suggesting release of factors by the tumor that may affect hearing, possibly by a toxic effect on the cochlear nerve.

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Figure 1.

A 2.5 mm. NF2 invasive bud (t) in wall of internal auditory canal following translabyrinthine removal of large vestibular nerve schwannoma (hTB#211, left) (A). Solitary schwannoma (s) in internal auditory canal near the anterior basal segment of the cochlea (c); (nb) indicates new bone formation, possibly a reparative phenomenon (B). In contrast, an invasive NF2-related VS (#763, right) invades new bone (nb) extending from the IAC (C). An invasive bud can be seen nearly entering marrow spaces adjacent to the IAC (#57)(D). (Hematoxylin and Eosin X 40 (H&E X40))

Figure 2.

Schwannoma (s) spreading from the modiolus into fibrosis (f) in the anterior segment of the cochlea following a translabyrinthine removal of a vestibular nerve schwannoma (hTB#763, left). osl- osseous spiral lamina (A). Sporadic VS (s) originating in the modiolus without evidence of infiltration; anterior basal cochlear segment (c); osseous spiral lamina (osl) (B). An invasive NF2 VS can be seen infiltrating modiolar bone (arrow) at the base of the cochlea (#258, right)(C). An NF2-associated VS (#237, right) invading bone near the cochlear aqueduct (ca)(D). (H&E X100)

Figure 3.

Post contrast T1 weighted image (T1WIpG) at the level of the right internal auditory canal (IAC) demonstrates a large cerebellopontine angle (CPA) mass, which expands the IAC. Note the focal erosion (arrow) of the mid portion of the anterior wall of the IAC (#763) (A). MRI (T1WIpG) demonstrates a mass with expansion of the left IAC (#815) and focal erosion (arrow) of the posterior wall of the IAC (B).

Table 1

Patient characteristics and temporal bone findings.

	Case #	Age at Death	Sex	Right			Left		
				IAC Invasion	Surg.	Tumor Size (cm)	IAC Invasion	Surg.	Tumor Size (cm)
NF2 Severe ('Wishart')	22	31	F	Yes	MF	2	N/A	N/A	N/A
	57	21	F	Yes	No	9	Yes	MF	2.5
	211	52	M	Yes	TL	2.5	Yes	TL	2.0
	237	31	F	Yes	No	2.5	Yes	TL	1.0
	254	17	F	Yes	SO	4	Yes	SO	6.0
	255	34	F	No	RS	3.5	Yes	TL	3.0
	258	19	M	Yes	TL	3	No	RL	6.0
	350	53	M	Yes	No	3	N/A		3.5
	702	41	M	N/A	SO	5	Yes	TL	3.5
	763	36	M	Yes	No	N/A	Yes	TL	4.5
	815	50	M	N/A			Yes	SO	6
NF2 Mild ('Gardner')	650	70	M	No	No	0.6	No	No	2
Sporadic VS	156	71	F	No	MF	2			
	279	77	M	No	TL	3			
	299	72	F	No	TL	0.6			
	378	62	F	No	TL	3.5			
	612	92	F				No	SO	2.5
	44	61	F	No	TL	2			
	130	93	M	No	No	0.6			
	625	76	F	No	No	0.5			
	655	90	F				No	TL	2.5
	669	95	F	No	TL	2.5			
	712	94	F	No	No	0.2			
	633	87	M				No	TL	1.5
	223	84	F	No	No	0.4			
IAC=Internal Auditory Canal; N/A = Not available; TL=Translabyrinthine; SO=Suboccipital; RL=Retrolabyrinthine									

Table 2

Comparison of subject characteristics and temporal bone findings between the severe NF2 phenotype (“Wishart”) and sporadic VS groups.

	NF2 (Severe phenotype)	Sporadic VS	Statistical Significance
Age at death: Mean (SD) (by case)	34.1 (13.0)	81.1 (12.0)	p .001
Sex: % F/M (by case)	50.0%/50.0%	76.9%/23.1%	NS (p .10)
Size tumor: Mean (SD)	3.8 (1.96)	1.7 (1.1)	p .002
Invasion of IAC: %	88.9%	0.0%	p .001
Residual tumor in IAC: %	67%	60%	NS
Tumor Recurrence rate: %	22%	0%	NS (p .10)

F = female; M = male; SD = standard deviation; NS = not significant

Table 3

Hearing results for the NF2 (severe) versus sporadic VS groups: thresholds at each frequency tested, including pure tone averages (PTA) and speech discrimination scores (SDS).

Testing parameter	Mean threshold in dB (SEM)		Statistics (t-test)		
	IAC invasion (n=16)	No IAC invasion (n=15)	95% confidence interval:		P value
			lower	upper	
250 Hz	83.13 (8.849)	45.67 (8.322)	-62.380	-12.536	0.005*
500 Hz	81.56 (9.384)	45.67 (8.520)	-61.930	-9.862	0.009*
1000 Hz	79.69 (10.272)	51.67 (7.679)	-54.526	-1.516	0.039*
2000 Hz	86.56 (9.69)	59.33 (6.829)	-51.772	-2.687	0.031*
3000 Hz	94.69 (9.612)	70.67 (7.636)	-24.02	-49.343	0.062
4000 Hz	93.75 (9.869)	78.67 (7.375)	-15.08	-40.546	0.235
6000 Hz	95.00 (10.448)	80.77 (8.804)	-14.23	-43.083	0.321
PTA	85.625 (9.3868)	56.833 (7.1442)	-28.792	-53.1572	0.054
SDS (%)	30.27% (10.121)	63.08% (11.012)	32.81	2.096	0.037*

Hz = Hertz; dB = decibel hearing level; SEM = standard error of the mean; IAC = internal auditory canal;

* = statistically significant ($p < 0.05$)