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What is This?
Audiovestibular Characteristics of Small Cochleovestibular Schwannomas in Neurofibromatosis Type 2

Michael A. Holliday, MD1*, Hung Jeffrey Kim, MD1,2*, Christopher K. Zalewski, PhD3, Talah Wafa, AuD3, Ramita Dewan4, Kelly A. King, PhD3, Carmen C. Brewer, PhD3, John A. Butman, MD, PhD5, and Ashok R. Asthagiri, MD4

Abstract

Objective. Describe the relationship between cochleovestibular schwannoma (CVS) volume, audiovestibular characteristics, and magnetic resonance imaging (MRI) findings in patients with neurofibromatosis type 2 (NF2).

Study Design. Subgroup analysis of NF2 prospective natural history study from 2008 to 2011.

Setting. Quaternary medical research institute.

Subjects and Methods. NF2 patients with small treatment-naive CVSs (volume <1000 mm³) by ear; N = 49 ears (32 patients). Cross-sectional analysis of the following parameters was performed: tumor size, auditory brainstem response (ABR), 4-frequency pure-tone average (4f-PTA; 0.5, 1, 2, and 4KHz), cervical vestibular evoked myogenic potential (cVEMP), caloric testing, 240° velocity step test (VST), and MRI findings.

Results. For all physiologic measures but the 4f-PTA, larger tumors correlated with abnormal responses (P < .05). For abnormal ABR, mean tumor volume was 405 vs 151 mm³ (P = .0007) for normal ABR. Similarly, larger tumors correlated with weak caloric responses (mean 521 vs 165 mm³; P = .0007) and weak cVEMP (mean 357 vs 192 mm³; P = .0262). Tumor volume was not significantly correlated with 4f-PTA. Elevated intralabyrinthine protein on MRI fluid-attenuated inversion recovery sequences was correlated with larger tumor volume (mean 333 vs 55 mm³; P = .001) and abnormal ABR and 4f-PTA (P < .05) but did not correlate with cVEMP, VST, or caloric responses.

Conclusion. In our cohort, ABR, caloric response, cVEMP, and elevated intralabyrinthine protein correlated with tumor volume, but 4f-PTA did not. Abnormal ABR and 4f-PTA correlated with elevated intralabyrinthine protein. These findings may provide insight on the effect of small CVS on the inner ear and cochleovestibular nerves, which may aid in their optimal management.

Keywords

neurofibromatosis type 2, audiogram, ABER, ABR, vestibular tests, VEMP, caloric tests, MRI

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Neurofibromatosis type 2 (NF2) is a hereditary multiple neoplasia syndrome characterized by bilateral cochleovestibular schwannomas (CVSs) and other nervous system tumors. Unlike sporadic CVSs, NF2-related CVSs have unpredictable growth patterns and progression of symptoms. The bilaterality of tumors in NF2 precludes comparing clinical findings with a “control” contralateral ear, and tumor growth and phenotype between sides in the same patient are often unrelated.

Patients with NF2 often present with hearing loss, which may be accompanied by tinnitus, dizziness, or imbalance. There is no standard approach to management of CVSs

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related to NF2, and treatment is individualized to the patient and specific ear. In the absence of brainstem compression, the approach is often watchful waiting, but there is no consensus regarding timing of treatment with surgery, chemotherapy, or radiation therapy. It is still unclear whether to wait until further tumor growth, hearing loss, or both to pursue surgery for smaller tumors.

Observation with periodic imaging and audiologic evaluation is a common conservative option for managing small tumors, with vestibular phenotype not routinely addressed. An alternative strategy is an “early proactive” or “hearing conservation” approach, rather than watchful waiting, wherein the CVS is removed soon after detection to preempt further hearing loss with tumor progression. In experienced centers, removal of NF2 CVSs yields hearing preservation rates of 42% to 63%—lower than rates after sporadic tumor resection—but tumor recurrence rate within the surgical bed remains high at 58% for small tumor resection, reflecting the multifocality and infiltrating nature of NF2 CVSs. NF2 patients have higher rates of surgical intervention than unilateral sporadic CVSs, but the optimal time to intervene has not been firmly established, especially for small tumors less than 1.5 cm.

A recent study of 87 untreated NF2 CVSs showed that the presence of hearing loss strongly correlated with elevated intralabyrinthine protein in the inner ear, as identified by fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). Hearing loss was identified even in small CVSs, as nearly 50% of tumors less than 0.5 cm³ were associated with blockage of the cochlear aperture and elevated protein.

The current study was designed to characterize the audiometric and vestibular characteristics of small (≤1000 mm³) CVSs mostly contained within the internal auditory canal (IAC). We also sought to correlate MRI findings—namely, tumor volume, elevated intralabyrinthine protein, and cochlear aperture obstruction—with audiovestibular findings. Likewise, we attempted to identify any intralabyrinthine components of the tumors. This information may help elucidate the optimal timing and outcome of CVS treatment in NF2.

**Patients and Methods**

**Patients**

Audiovestibular, clinical, and imaging data were gathered from patients enrolled in a National Institutes of Health (NIH) NF2 natural history study (08-N-0044), approved by the Combined Neuroscience Institutional Review Board. NF2 was diagnosed in these patients by clinical and/or genetic criteria. Ears with treatment-naive CVSs less than 1000 mm³ (intracanalicular and posterior fossa components combined) were included in the study. This sample is a subset of tumors of all sizes recently studied by Asthagiri et al. Patients with middle ear disease, unreliable testing, or familial nonsyndromic hearing loss were excluded from analysis.

**Clinical Evaluation**

Detailed histories were obtained, and comprehensive otologic and neurologic examinations were conducted by a neurologist (H.J.K.) and a neurosurgeon (A.R.A.).

**Audiometric Evaluation**

Concurrent audiometric evaluations were performed on all patients, and included air and bone conduction thresholds from 250 to 8000 Hz and 250 to 4000 Hz, respectively. Hearing was analyzed using a 4-frequency (0.5, 1, 2, and 4 kHz) air-conducted pure-tone average (4f-PTA) as normal hearing (4f-PTA ≤20 dB hearing level [HL]) or the presence of hearing loss (4f-PTA >20 dB HL). Ears with a conductive hearing loss component (>10 dB average air-bone gap) were excluded.

**Electrophysiologic Evaluation**

Auditory brainstem response (ABR) was measured to rarefaction and condensation clicks using 85 dB normal HL (nHL) or 95 dB nHL at 8.3 c/s (Audera, Grason-Stadler, Eden Prairie, Minnesota). Auditory brainstem responses were graded 0 to 4 by audiologists (C.K.Z., K.A.K., and C.C.B.) with respect to wave presence, morphology, peak-interpeak latencies, and amplitude ratios (Table 1). Grades 1 to 2 were considered normal; grades 3 to 4 were considered abnormal and consistent with retrocochlear dysfunction; grade 0 reflected an absent or grossly abnormal ABR due to peripheral hearing confounds (sensorineural hearing loss >70 dB HL at 4 kHz).

**Vestibular Evaluation**

Only patients with bilateral treatment-naive ears received a comprehensive vestibular assessment, including tests known to lateralize abnormalities: cervical vestibular evoked myogenic potentials (cVEMP), rotational testing via velocity step testing at 240°/s (VST), and caloric testing. The cVEMPs were recorded using a 500-Hz tone burst stimulus presented via insert phones at 100 dB nHL or 107 dB nHL, 5.1 bursts per second (Smart EP Intelligent Hearing Systems, Miami, Florida). Response data were accepted when sternocleidomastoid activation levels were 50 to 100 μV. cVEMP was considered abnormal when P1-N1 was absent or if amplitude was <28 μV (107 dB) or <10 μV (100 dB) (C.K.Z., K.A.K., C.C.B., unpublished normative data).

Rotational VST employed 200°/s² acceleration to 240°/s rightward and leftward constant rotational velocity with infrared binocular eye tracking (Neuro Kinetics NOTC Suite; VEST Software, Pittsburgh, Pennsylvania). Peak eye velocity was calculated for the per- and postrotatory conditions in each direction. An abnormal result was identified for per-rotary peak velocity <50°/s.

Caloric irrigations were conducted using air stimulation at 24°C (cool) and 50°C (warm) with videonystagmography. The peak slow-phase velocity (SPV) component of nystagmus was measured for each irrigation. Total SPV response
for each ear (warm and cool irrigation) \(<12^\circ\text{s}\) was interpreted as ear-specific hypofunction.\(^{14}\)

### Imaging Evaluation

Patients underwent MRI with or without contrast of the craniospinal axis (*Figure 1A*). Imaging was interpreted by a neuroradiologist (J.A.B.), blinded to the audiovestibular status of individual ears. Inner ear MRI was performed with \(<1\text{-mm}\) in-plane resolution using a 3T MR-scanner (Philips, Andover, Massachusetts). Non–contrast-enhanced FLAIR sequences were performed to detect elevated intralabyrinthine protein within the inner ear, appearing isointense compared with the brain (*Figure 1B*).\(^{15}\) T2-3D TSE with Variable Flip Angle (VISTA) magnetic resonance images were performed to detect cochlear aperture obstruction, as defined by the absence of a patent cerebrospinal fluid (CSF) pathway between the posterior fossa and the cochlear aperture (cochlear nerve entry point into the modiolus) (*Figure 1C*).\(^{10}\)

Volume of the tumors was determined using postcontrast T1-weighted images and the following formula: volume = \(\frac{(\text{maximum anteroposterior dimension} \times \text{maximum mediolateral dimension} \times \text{maximum craniocaudal dimension})}{2}\).\(^{16,17}\) Canalicular and posterior fossa components, if present, were summed for total CVS volume. Displacement of fluid signal on T2-VISTA sequences identified small discrete intralabyrinthine tumors.\(^{10}\)

### Statistical Analysis

Statistical analyses were performed using GraphPad Prism Version 6.01 (GraphPad Software, La Jolla, California). The Fisher exact test was used for analysis of association between binary variables. The Mann-Whitney test was used for association of a binary variable to a continuous variable. \(P < .05\) was considered significant.

### Results

#### Patient Demographics

Fifty-three ears (34 patients) in the National Institutes of Health study group met volume criteria. One patient (2 ears) was excluded due to excessive ocular recording artifact. Another patient (2 ears) was excluded for non–NF2-related familial hearing loss. Therefore, a total of 32 patients (\(N = 49\) ears) were used in this analysis. Females outnumbered males approximately 3 to 1, and males were significantly

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**Table 1. ABR Grading Scale for National Institutes of Health Neurofibromatosis Type 2 Natural History Study.**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
</tr>
<tr>
<td>2</td>
<td>Borderline normal</td>
</tr>
<tr>
<td>3</td>
<td>Abnormal retrocochlear</td>
</tr>
<tr>
<td>4</td>
<td>Abnormal retrocochlear gross</td>
</tr>
<tr>
<td>0</td>
<td>Abnormal with peripheral confounds</td>
</tr>
</tbody>
</table>

All waves present with good morphology, absolute latencies, IPLs, ILD V, and V/I amplitude ratio all WNL

Normal IPLs; does not meet criteria for grade 1

Absent I and/or III in presence of normal wave V latency, OR

Absolute latency delay for wave I and/or III, with normal wave V latency and normal IPL, OR

Abnormal V/I amplitude ratio with normal absolute latencies and IPLs, OR

Waves I, III, and V with absolute latencies and IPLs WNL, but poor morphology, OR

Normal absolute latency I and III with prolonged V, normal IPL

Present I, III, and V with prolonged IPL and normal or abnormal absolute latency, OR

Absent wave I and/or III and prolonged V with hearing thresholds of 70 dB HL or better

Absent V (required)

All waves absent and hearing better than 70 dB HL OR

Wave I only or Waves I and III only

Absence of all waves with hearing >70 dB HL

Absence of I and/or III and prolonged V with hearing thresholds >70 dB HL

---

Abbreviations: HL, hearing level; ILD, interaural latency difference; IPL, interpeak latency; WNL, within normal limits

---

**Figure 1.** Magnetic resonance imaging of the left internal auditory canal (IAC) tumor in sample. (A) T1 post-gadolinium showing tumor volume of 287.8 mm\(^3\) (arrow). (B) Fluid-attenuated inversion recovery sequence showing elevated protein in basal turn of left cochlea (arrow). (C) T2 VISTA reveals cochlear aperture obstruction without fluid in distal IAC (arrow).
younger than females (Table 2, P < .0001). In 17 patients (53.1%), bilateral CVSs met inclusion criteria for the study.

### Tumor Volume and Location

Tumor volume ranged from 1 mm$^3$ (smallest perceptible tumor, unable to measure) to 923.8 mm$^3$ (Figure 2). Tumor volume did not significantly differ between sex and side of lesion. Five ears had intralabyrinthine schwannoma identified by MRI—3 in the vestibule and 2 in the cochlea—which did not correlate with their respective audiovestibular tests. Association of volume with each test is discussed individually below.

### Pure-Tone Audiometry

Pure-tone audiometry was performed for all 49 study ears. Average 4t-PTA among the study group was 22.8 dB HL (range, 1.25-95). Hearing loss was present in 17 ears (34.7%) but did not correlate with tumor volume ($P = .0756$; Mann-Whitney) (Table 3 and Figure 3).

### Auditory Brainstem Response

Auditory brainstem response was performed for all 49 study ears. There were 32 ears with normal ABR (grades 1-2) and 17 ears with abnormal ABR (grades 0, 3-4). Ears with abnormal ABR findings had a larger tumor volume (404 vs 151 mm$^3$; $P = .0007$) (Table 3 and Figure 3).

### Vestibular Testing

Abnormal cVEMP and caloric testing were significantly associated with larger tumor size (Figure 4). Velocity step testing was abnormal in only 1 ear, which had the largest tumor in the study (923 mm$^3$). For patients who completed cVEMP and caloric testing ($n = 32$), 5 ears had abnormal responses to both tests, while 5 ears had only weak cVEMP and 2 ears had only caloric weakness (Table 4).

Patients with subjective complaints of vertigo or disequilibrium tended to have abnormal cVEMP responses ($P = .0280$, Fisher exact test) but did not have abnormal caloric testing ($P = .6691$, Fisher exact test).

### Radiographic Findings

Elevated intralabyrinthine protein was noted on FLAIR sequence MRI in 34 of 49 ears (69%), which correlated with hearing loss and abnormal ABR ($P < .05$; Table 3). Cochlear aperture obstruction was observed in 34 of 49 cases (69%), which correlated with larger tumors, increased intralabyrinthine protein, and abnormal ABR and cVEMP testing ($P < .05$; Table 3).

### Discussion

NF2-related tumors constitute less than 5% of all CVSs and differ in behavior and phenotype from the sporadic type. Histopathologically, NF2-related tumors exhibit multicentricity (73%), labyrinth involvement (88%), facial nerve involvement (58%), and “fusion” with adjacent tumors—distinguishing them from sporadic schwannomas.

Intracochlear lesions and facial nerve invasion occur as well. This contrasts with Roosli and colleagues’ analysis of 50 sporadic CVSs, in which the tumor was found to arise from single identifiable foci—the vestibular nerve or branches in 76% of ears or the cochlear nerve in 24%.

The relationships among MRI findings (tumor size, intralabyrinthine protein, and cochlear aperture obstruction), hearing loss, and vestibular function have not been described previously for small treatment-naive CVSs in NF2 patients.

### Audiometric/Electrophysiologic Evaluation

Among our cohort of NF2 patients with small tumors, abnormal ABR findings and vestibular studies were

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### Table 2. Participant Demographics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of ears</td>
<td>49</td>
</tr>
<tr>
<td>No. of patients</td>
<td>32</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23 (71.9)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (28.1)</td>
</tr>
<tr>
<td>Bilateral small CVS</td>
<td>17 (53.1)</td>
</tr>
<tr>
<td>Unilateral small CVS</td>
<td>15 (46.9)</td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>28.2 (8-68)</td>
</tr>
<tr>
<td>Female (mean age), y</td>
<td>35.6</td>
</tr>
<tr>
<td>Male (mean age), y</td>
<td>17.3</td>
</tr>
<tr>
<td>Tumor volume, mm$^3$</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>247.8 (246.7)</td>
</tr>
<tr>
<td>Range</td>
<td>1-923.8</td>
</tr>
</tbody>
</table>

Abbreviation: CVS, cochleovestibular schwannoma.

*Values are presented as number (%) unless otherwise indicated.

---

Figure 2. Scatter dot plot of tumor volumes included in study.

Figure 3. Mean + SD and mean 247.8.
associated with larger tumors, but the association was not present for 4f-PTA. The lack of association of hearing sensitivity with tumor size is consistent with prior studies at our institution and others examining tumors of all sizes.10,11,21 However, a prior NF2 natural history study revealed that increasing size (<1.5 cm vs 1.5-3 cm vs >3 cm) correlated with worsening mid- and high-frequency averages, speech reception thresholds, and abnormal ABR.9 What features of the tumor, if not size, determine audiometric abnormalities? Perhaps increased intralabyrinthine protein,22 the infiltrative nature of smaller tumors,19 and/or the presence of undetectable intracochlear schwannomas19 may be responsible for hearing loss, rather than compression or ischemia of the nerve by increasingly larger tumors.

Among our cohort, abnormal ABRs correlated with larger tumor volume; nevertheless, normal ABRs occurred in tumors up to 792 mm³ (Figure 3), thus yielding a 72.7% false-negative rate, exceeding a false-negative rate of 42% for sporadic CVSs.23 This may be due to earlier surveillance, and hence diagnosis, of NF2 tumors in a familial condition. On the other hand, some ears with tumors as small as 43 mm³ showed ABR abnormalities. These findings confirm that ABR is not a satisfactory method for detection of small CVSs.23 Yet for known NF2, neither tumor size nor growth rate provides absolute criteria for surgical intervention, particularly in the face of serviceable hearing. Physiologic measures such as ABR may therefore serve a role in surveillance of clinical progression through detection of subtle retrocochlear changes, or perhaps new foci of tumor in the auditory pathway. It remains to be seen whether the transition to abnormal ABR signals a threshold before hearing diminishes significantly, which may better inform timing for surgical intervention.

**Vestibular Evaluation**

For each vestibular test in this study, abnormal findings were associated with larger tumor volume (Table 3 and Figure 4), similar to studies of sporadic tumors.24 Due to the bilateral nature of NF2, this likely leads to significant bilateral vestibular dysfunction as tumor burden increases.

### Table 3. Results of Electrophysiologic, Audiometric, and Vestibular Testing, Along with Radiographic Findings.

<table>
<thead>
<tr>
<th></th>
<th>Total Ears, %</th>
<th>Normal</th>
<th>Abnormal</th>
<th>Correlation with Size</th>
<th>Correlation with Intralabyrinthine Protein</th>
<th>Correlation with CAO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Mean Volume (95% CI), mm³</td>
<td>No. (%)</td>
<td>Mean Volume (95% CI), mm³</td>
<td>Yes or No</td>
<td>P Value</td>
</tr>
<tr>
<td>Electrophysiologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ABR</td>
<td>49 (100)</td>
<td>32 (65.3)</td>
<td>151.3 (89.6-213)</td>
<td>17 (34.7)</td>
<td>405.0 (264-546)</td>
<td>Yes</td>
</tr>
<tr>
<td>Audiometric</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4f-PTA</td>
<td>49 (100)</td>
<td>32 (65.3)</td>
<td>227.9 (129-327)</td>
<td>17 (34.7)</td>
<td>285.2 (192-379)</td>
<td>No</td>
</tr>
<tr>
<td>Vestibular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cVEMP</td>
<td>38 (77.6)</td>
<td>27 (71.1)</td>
<td>191.6 (96.7-287)</td>
<td>11 (28.9)</td>
<td>356.9 (184-530)</td>
<td>Yes</td>
</tr>
<tr>
<td>Caloric</td>
<td>32 (65.3)</td>
<td>25 (78.1)</td>
<td>164.8 (95.7-234)</td>
<td>7 (21.9)</td>
<td>520.7 (300-741)</td>
<td>Yes</td>
</tr>
<tr>
<td>VST</td>
<td>30 (61.2)</td>
<td>29 (96.7)</td>
<td>262.9 (173-353)</td>
<td>1 (3.3)</td>
<td>923.8 NA</td>
<td>NA</td>
</tr>
<tr>
<td>Radiographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAO</td>
<td>49 (100)</td>
<td>15 (30.1)</td>
<td>43.4 (19.0-67.8)</td>
<td>34 (69.4)</td>
<td>337.9 (252-423)</td>
<td>Yes</td>
</tr>
<tr>
<td>Elevated intralabyrinthine protein</td>
<td>49 (100)</td>
<td>15 (30.1)</td>
<td>55.48 (8.17-103)</td>
<td>34 (69.4)</td>
<td>326.2 (246-419)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Abbreviations:** ABR, auditory brainstem response; CAO, cochlear aperture obstruction; CI, confidence interval; cVEMP, cervical vestibular evoked myogenic potential; 4f-PTA, 4-frequency pure-tone average; NA, not applicable; VST, velocity step test at 240°/s.

*^Mann-Whitney test.

*^Fisher exact test.

**Figure 3.** Tumor volume (mean, 95% confidence interval) in ears showing abnormal audiometric and auditory brainstem responses (ABR) (gray) and normal responses (white). Difference was not significant for pure-tone audiometry (P = .0756) but was significant for ABR (P = .0007).
obstruction and abnormalities in each test. This neurovascular relationship supplied by the anterior vestibular artery, a separate branch of the labyrinthine artery—the common cochlear artery—while the horizontal semicircular canal is the same branch of the labyrinthine artery—the common cochlear artery. Within the vestibular testing battery, only cVEMP was associated with cochlear aperture obstruction. Since cochlear aperture obstruction was also associated with 4f-PTA and ABR changes, this suggests that tumor extending to the meatal foramen displacing the CSF in the distal IAC is more likely to affect inferiorly traveling cochlear nerve and inferior vestibular nerve by directly applying pressure on the nerves or on the blood supply to the cochlea and saccule. Indeed, intracanalicular pressure measurements have been correlated with the extension of tumor into the IAC as well.25 In addition, intracanalicular pressure measurements have been correlated with the extension of tumor into the IAC as well.25 In addition, intracanalicular pressure measurements have been correlated with the extension of tumor into the IAC as well.

Elevated Intralabyrinthine Protein

Reflecting their presumed effect on hearing function, we found that cochlear aperture obstruction and elevated intralabyrinthine protein are significantly associated with hearing loss and abnormal ABR (Table 3). Asthagiri and colleagues previously reported similar findings among a wider NF2 study group with tumors of all sizes and including many of the tumors from the current study. Elevated protein correlated with hearing loss and was hypothesized to be an important etiologic factor for such hearing loss in NF2 tumors. Protein/cytokines, or mechanical obstruction of the cochlear aperture limiting protein clearance.

In the present study, we sought to examine small tumors to further delineate the influence of intralabyrinthine protein, while controlling for large, compressive tumors. We found a significant association between elevated intralabyrinthine protein and hearing loss (P = .0352), yet 18 ears (36.7%) had elevated protein with normal hearing. We found a similar association between elevated protein and abnormal ABR (P = .0082), yet another 18 ears (36.7%) had elevated protein with normal ABR. Longitudinal study will help determine if those ears with normal ABR/audiometry and elevated protein eventually develop abnormal ABR or hearing loss. If a causal relationship between elevated protein and clinical features can be elucidated, this may be the window for intervention.

Unlike audiologic testing, increased intralabyrinthine protein on MRI did not correlate with abnormal vestibular testing. In this study, the labyrinth was simply scored for the presence or absence of FLAIR signal abnormality indicative of protein accumulation, rather than a compartmental analysis of protein distribution. Therefore, we cannot say whether there was differential involvement of the auditory or vestibular components of the labyrinth by this process. In addition, FLAIR changes may be more difficult to detect in the vestibular organ due to the small volume of the perilymph in the semicircular canals and vestibule compared with the cochlea.

Table 3. Comparison of cVEMP and Caloric Test Findings.

<table>
<thead>
<tr>
<th>Test</th>
<th>No. (%) of Ears</th>
</tr>
</thead>
<tbody>
<tr>
<td>cVEMP and caloric testing</td>
<td>32 (100)</td>
</tr>
<tr>
<td>Normal cVEMP, normal caloric</td>
<td>20 (62.5)</td>
</tr>
<tr>
<td>Abnormal cVEMP, normal caloric</td>
<td>5 (15.6)</td>
</tr>
<tr>
<td>Normal cVEMP, abnormal caloric</td>
<td>2 (6.3)</td>
</tr>
<tr>
<td>Abnormal cVEMP, abnormal caloric</td>
<td>5 (15.6)</td>
</tr>
</tbody>
</table>

Abbreviation: cVEMP, cervical vestibular evoked myogenic potential.

Intralabyrinthine Tumors

In the current study, the 5 ears with intralabyrinthine tumor components were not significantly associated with abnormal audiovestibular testing. However, elevated intralabyrinthine protein was found in all 5 ears. The presence of intralabyrinthine tumors may contribute to the unexpected lower short- and long-term hearing preservation rate in NF2 CVSs reported at experienced centers, compared with sporadic tumors.6

Careful examination of MRI for intralabyrinthine tumors may therefore have a significant effect on treatment planning when a hearing preservation resection is considered, although many tiny intralabyrinthine tumors are undetectable even by currently available MRI. Among a relatively large population of 89 NF2 ears, fewer than 15% showed intralabyrinthine tumor presence on thin-cut 3T MRI,10 compared with 88% of ears with intralabyrinthine tumors in the largest histopathologic study.19

Predicting Tumor Origin

Each nerve within the IAC has corresponding audiometric, vestibular, or clinical findings, suggesting that audiovestibular...
data may provide topographical insight into the nerve of origin or the nerve under compression or invasion. Abnormal caloric and VST reflect superior vestibular nerve (SVN) involvement by the tumor, whereas abnormal cVEMP signifies involvement of the IVN. Abnormal ABR and 4f-PTA reveal involvement of the cochlear nerve and inner ear, respectively.

In a series of 7 NF2 ears with preoperative vestibular testing, Rosengren et al. reported 1 ear (14%) with absent cVEMP and 5 (71%) with abnormal caloric responses, implying that the SVN is affected more often than the IVN. However, the multicentricity and invasiveness of NF2 CVSs may preclude an elegant prediction of a single nerve of origin based on audiovestibular testing, as in cases of unilateral sporadic CVS.

**Limitations**

This study is limited by the cross-sectional design and small sample, particularly for vestibular analysis. In this study, comprehensive vestibular tests were performed only in patients with 2 treatment-naive ears, and many of the patients in the broader natural history study have had surgery on at least 1 ear. The selection of treatment-naive CVSs may have also resulted in a selection bias for evaluating less aggressive tumors. Results may also be affected by familial relationships within the group.

Future studies will assess the longitudinal progression of audiovestibular data and MRI characteristics. These studies may reveal onset or progression of hearing loss in those ears with elevated protein, which may support the theory of elevated intralabyrinthine protein as a mechanism of hearing loss. If surgery is performed on these ears, the nerve of origin, if identified, may also be correlated to preoperative audiovestibular findings.

**Conclusion**

When patients with NF2 are managed conservatively with serial surveillance, ABR, and vestibular testing in addition to MRI and PTA, this may assist in evaluating the functional implications of CVSs. These tests may reflect increased growth and the infiltrating nature of CVSs in conjunction with MRI, but more investigation is needed to determine these changes over time. Although MRI accurately determines tumor size, as well as growth rate with serial MRI, the lack of a clear size threshold for symptom progression precludes strict size criteria as a determining factor for intervention. If physiologic audiovestibular tests, along with MRI assessment of intralabyrinthine protein and cochlear aperture obstruction, can anticipate the development and progression of symptoms, then they may help determine the optimal timing of intervention.

**Author Contributions**

Michael A. Holliday, data analysis/interpretation, drafting article, final approval; Hung Jeffrey Kim, conception/design, data analysis/interpretation, drafting and revising article, final approval; Christopher K. Zalewski, conception/design, data acquisition, data analysis, critical article revision, final approval; Talah Wafa, data acquisition, data analysis, critical article revision, final approval; Ramita Dewan, data acquisition, data analysis, critical article revision, final approval; Kelly A. King, conception/design, data acquisition, data analysis, critical article revision, final approval; Carmen C. Brewer, conception/design, data acquisition, data analysis, critical article revision, final approval; John A. Butman, conception/design, data acquisition, data analysis/interpretation, critical article revision, final approval; Ashok R. Asthagiri, conception/design, data analysis/interpretation, critical article revision, final approval.

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