

Mechanisms of Morbid Hearing Loss Associated With Tumors of the Endolymphatic Sac in von Hippel-Lindau Disease

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ENDOLYMPHATIC SAC TUMORS (ELSTs) are highly vascular, benign, but locally aggressive neoplasms of the endolymphatic system that often destroy the surrounding temporal bone (FIGURE 1).¹⁻³ ELSTs occur sporadically but are a common manifestation of von Hippel-Lindau disease (VHL), in which they can also occur bilaterally.^{3,4} ELSTs are associated with significant audiovestibular morbidity, including sudden irreversible hearing loss.³⁻⁵ Despite the effects of ELSTs and their association with VHL, the underlying pathophysiologic mechanisms of audiovestibular dysfunction associated with ELSTs, the high incidence of unexplained audiovestibular dysfunction in patients with VHL, and the optimal timing of treatment for ELSTs have not been defined.

Since clinicians have determined the presence of ELSTs in the VHL syndrome, prospective screening proto-

See also Patient Page.

Context Endolymphatic sac tumors (ELSTs) are associated with von Hippel-Lindau disease and cause irreversible sensorineural hearing loss (SNHL) and vestibulopathy. The underlying mechanisms of audiovestibular morbidity remain unclear and optimal timing of treatment is not known.

Objective To define the mechanisms underlying audiovestibular pathophysiology associated with ELSTs.

Design, Setting, and Patients Prospective and serial evaluation of patients with von Hippel-Lindau disease and ELSTs at the National Institutes of Health between May 1990 and December 2006.

Main Outcome Measures Clinical findings and audiologic data were correlated with serial magnetic resonance imaging and computed tomography imaging studies to determine mechanisms underlying audiovestibular dysfunction.

Results Thirty-five patients with von Hippel-Lindau disease and ELSTs in 38 ears (3 bilateral ELSTs) were identified. Tumor invasion of the otic capsule was associated with larger tumors ($P=.01$) and occurred in 7 ears (18%) causing SNHL (100%). No evidence of otic capsule invasion was present in the remaining 31 ears (82%). SNHL developed in 27 of these 31 ears (87%) either suddenly (14 ears; 52%) or gradually (13 ears; 48%) and 4 ears had normal hearing. Intralabyrinthine hemorrhage was found in 11 of 14 ears with sudden SNHL (79%; $P<.001$) but occurred in none of the 17 ears with gradual SNHL or normal hearing. Tumor size was not related to SNHL ($P=.23$) or vestibulopathy ($P=.83$).

Conclusions ELST-associated SNHL and vestibulopathy may occur suddenly due to tumor-associated intralabyrinthine hemorrhage, or insidiously, consistent with endolymphatic hydrops. Both of these pathophysiologic mechanisms occur with small tumors that are not associated with otic capsule invasion.

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cols in patients with VHL including serial high-resolution magnetic resonance imaging (MRI) and computed tomographic (CT) imaging with audiologic evaluations have been developed and used at the National Institutes of Health.

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Information from these evaluations now provides insight into the mechanisms of symptom formation, early imaging features, and the natural history of ELSTs. To determine the mechanisms underlying hearing loss and other ves-

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tibulopathy in patients with ELSTs, we analyzed the serial imaging and clinical findings in consecutive patients with VHL with ELSTs.

METHODS

Patients

Clinic charts, audiograms, MRI, and CT images were analyzed for patients with VHL whose cases were monitored at the National Institutes of Health between May 25, 1990, and December 18, 2006. All patients were studied under National Institute of Neurological Disorders and Stroke internal review board–approved protocols (NIH 79-N-0089 and NIH 00-N-0140) after providing informed consent. Patients were prospectively monitored for the development of audiovestibular symptoms and included if diagnostic imaging showed evidence of ELST.

Imaging Studies

Neuroradiologists blinded to the presence and degree of audiovestibular findings reviewed all imaging studies and recorded the results.

CT Imaging

To determine the presence of otic capsule invasion and extent of bony erosion by ELSTs, temporal bone CT imaging (axial and coronal; 0.625- to 1.5-mm slice thickness; bone algorithm reconstruction kernel) was performed. For analysis purposes, ELSTs were divided into 2 groups based on CT imaging evidence of otic capsule invasion by tumor or lack thereof.

Magnetic Resonance Imaging

Inner ear MRI was used to identify the extent of soft tissue mass in the temporal bone and to evaluate signal within the sensory labyrinth. Because the studies spanned several years, there was some variation in technique commensurate with technical improvements in methodology. Before 1999, MRI included spin echo T1-weighted precontrast and postcontrast and fast spin echo T2-weighted sequences using slice thickness of 3 mm or less. After 1999, examinations used 1.6-mm overlapping spoiled gradient recall T1-weighted precontrast and postcontrast, T2-weighted fast induction of

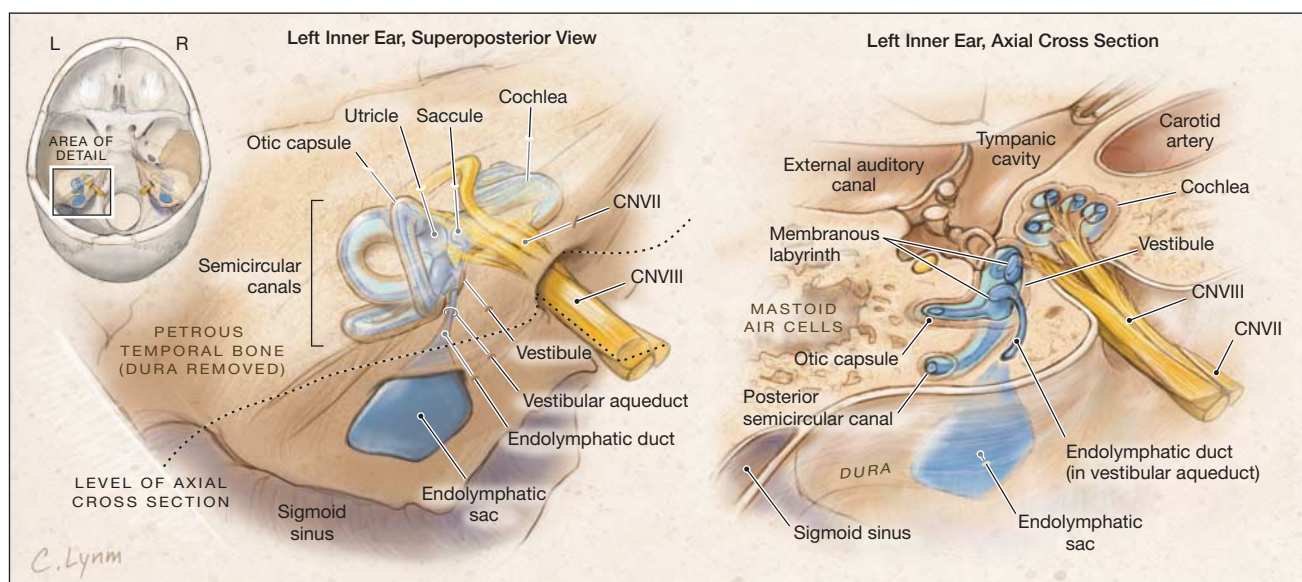
steady state acquisition, and 3- to 5-mm fluid-attenuated inversion recovery. Image resolution was less than 1 mm in plane in all cases.

Because the contents of the vestibular aqueduct may normally enhance on high-resolution postcontrast T1-weighted spoiled gradient recall sequences, small in situ ELSTs were identified by asymmetrical enhancement of the endolymphatic duct on MRI together with bony erosion of the vestibular aqueduct on CT imaging. The presence of intralabyrinthine hemorrhage was defined on MRI as abnormal isolated intralabyrinthine increased signal on precontrast T1-weighted images. Intralabyrinthine lipoma, which could also appear as a precontrast T1-weighted hyperintensity, was excluded on fat-saturated MRI. To quantify and compare tumor size, the largest tumor diameter was determined from a single axial slice using MRI and recorded.

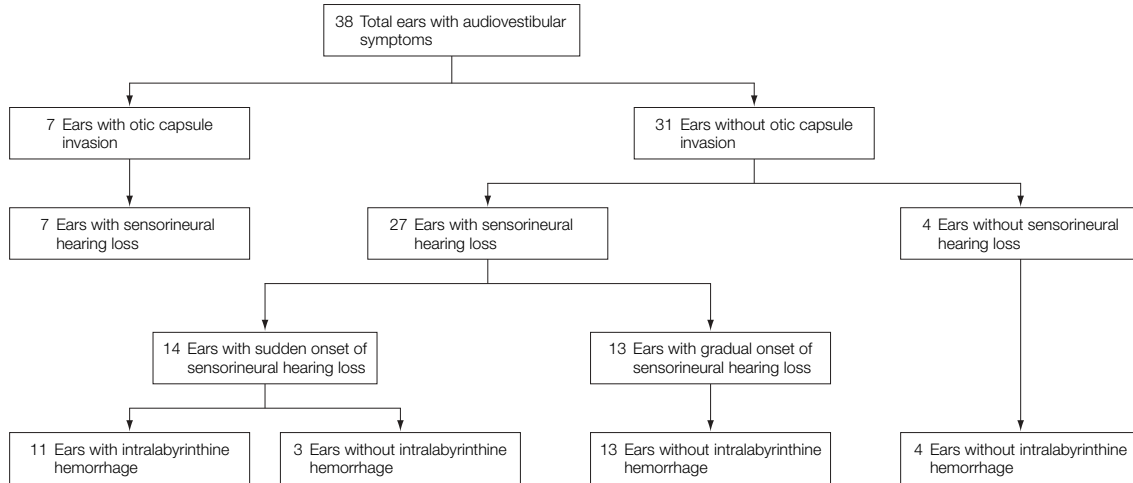
Clinical Evaluation

Patients underwent complete neurologic and audiologic examinations (see "Audio-

Figure 1. Anatomical Relationships of the Endolymphatic Sac



The endolymphatic sac is located on the posteromedial surface of the petrous temporal bone, covered by dura. The endolymphatic duct lies within the vestibular aqueduct and connects the endolymphatic sac to the remainder of the membranous labyrinth. The bony otic capsule encases the membranous labyrinth. Tumors of the endolymphatic sac can result in hearing loss directly through invasion of adjacent sensory structures housed within the otic capsule or indirectly through intralabyrinthine hemorrhage or endolymphatic hydrops. CN indicates cranial nerve.

Figure 2. Distribution of Ears With Endolymphatic Sac Tumors

Distribution of 38 ears based on history, imaging, and clinical findings affected by endolymphatic sac tumors in 35 consecutive patients with von Hippel-Lindau disease.

logic Assessment” section) at intervals of 6 to 24 months or when audiovestibular symptoms developed. The presence of audiovestibular symptoms including tinnitus, vertigo, aural fullness, and specific evidence of other cranial nerve abnormalities were recorded at each visit.

Audiologic Assessment

Audiometric evaluations were performed in conjunction with clinical evaluations and included air and bone conduction, pure tone thresholds, and speech discrimination assessment. Hearing loss was characterized as mild (26-40 dB), moderate (41-55 dB), moderate to severe (56-70 dB), severe (71-90 dB), or profound (≥ 91 dB). The time span over which the sensorineural hearing loss (SNHL) evolved was classified as sudden (<24 hours) or gradual (weeks-months). StatXact 6, version 6.2.0 (Cytel Inc, Cambridge, Massachusetts) and SPSS for Windows, version 11.5.0 (SPSS Inc, Chicago, Illinois). *P* level of significance was less than .05.

RESULTS

Overall Patient and Tumor Characteristics

A total of 38 ears affected by ELSTs (23 left [61%]; 15 right [39%]) were identified in 35 patients with VHL (19 fe-

male [54%]; 16 male [46%]; FIGURE 2). Bilateral ELSTs were detected in 3 patients (9%). Mean age (SD) at symptom onset was 31 (13) years (range, 11-63 years). Mean (SD) follow-up time was 7.78 (4.75) years (range, 0.25-16 years). All patients with imaging evidence of ELST developed audiovestibular symptoms including hearing loss, tinnitus, vertigo, aural fullness, aural pain, facial nerve weakness, or aural pain and facial nerve weakness combined (TABLE). Nineteen patients (54%) had a triad of the most common symptoms that included SNHL, tinnitus, and vertigo (9 additional patients [26%] had 2 of these symptoms). Mean tumor diameter (SD) was 1.4 cm (1.0 cm) (range, 0.2-5.2 cm). Tumor size was not associated with SNHL ($P = .23$) or with audiovestibular symptoms (analysis of variance; $P = .83$; FIGURE 3). Seven ears (6 patients; 18%; $P = .01$) had tumor-associated otic capsule invasion and 31 ears (30 patients; 82%) had no evidence of otic capsule invasion (Figure 2).

Ears With Otic Capsule Invasion

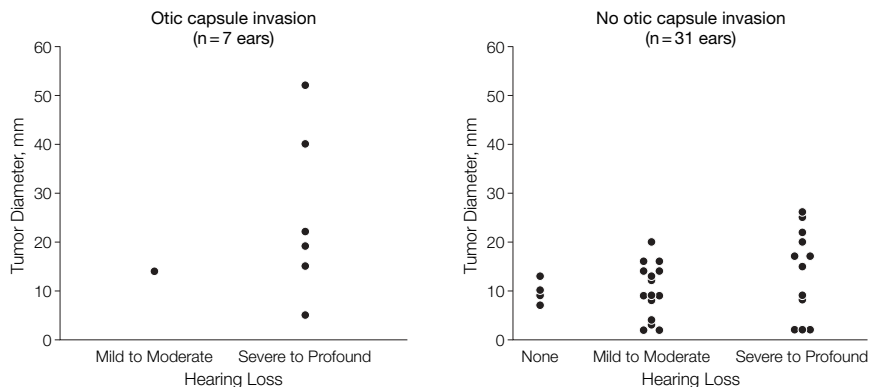
Clinical Findings. Seven ears (4 right; 3 left) among 6 patients (2 male; 4 female) had ELSTs that invaded the otic capsule. Two of these patients had bi-

Table. Findings in 38 Ears Affected by Endolymphatic Sac Tumors in 35 Patients With von Hippel-Lindau Disease

Finding	No. (%) ^a
Sex, No. (%) of patients	
Female	19 (54)
Male	16 (46)
Tumor location	
Left	23 (61)
Right	15 (39)
Bilateral	3 (9)
Otic capsule invasion	
Yes	7 (18)
No	31 (82)
Signs and symptoms	
Sensorineural hearing loss	34 (89)
None	4 (11)
Mild	6 (16)
Moderate	10 (26)
Profound	18 (47)
Tinnitus	27 (71)
Intermittent	14 (37)
Continuous	13 (34)
Vertigo	24 (69)
Intermittent	23 (85)
Continuous	4 (15)
Aural fullness	14 (37)
Intermittent	12 (32)
Continuous	2 (5)
Aural pain (continuous)	4 (11)
Facial nerve weakness (continuous)	2 (5)

^aData are for number of ears unless otherwise noted.

lateral ELSTs. One patient had unilateral invasion of the otic capsule and the other had bilateral invasion of the otic capsule. Mean (SD) age at audiovestibular symptom onset was 32 (13) years (range, 14-34 years). Overall, mean (SD) follow-up was 7.68 (4.43) years (range, 3.25-14.83 years).

Figure 3. Analysis of Correlation Between Tumor Size and Hearing Loss in Patients With von Hippel-Lindau Disease

Thirty-eight ears affected by endolymphatic sac tumors in 35 patients with von Hippel-Lindau disease were analyzed for correlation between tumor size and presence of sensorineural hearing loss. There was no correlation (analysis of variance; $P > .05$) between tumor size and sensorineural hearing loss in ears with or without otic capsule invasion.

When otic capsule invasion was detected, SNHL was present. The SNHL was mild in 1 ear and severe to profound in the remaining 6 ears (Figure 3). Additional audiovestibular and cranial nerve findings included vertigo (4 patients; 67%), tinnitus (4 ears; 57%), aural fullness (4 ears; 57%), facial nerve weakness (1 patient; 17%), and aural pain (1 ear; 14%). Vertigo was intermittent in all patients with vertigo (4; 100%). Tinnitus was continuous in 1 ear (25%) and intermittent in 3 ears (75%). Aural fullness was intermittent in all affected ears (4; 100%). Aural pain was continuous in the 1 affected patient (100%).

Imaging. All ELSTs with otic capsule invasion had the typical imaging features of ELST (FIGURE 4). Nonenhanced T1-weighted MRI revealed ELSTs as heterogeneous in intensity with associated areas of hyperintensity, suggestive of intratumoral hemorrhage and cholesterol granuloma formation (Figure 4). Precontrast isointense portions of the ELSTs enhanced on postcontrast T1-weighted MRI. ELSTs on CT imaging were isodense with gray matter, with foci of bone density indicating bone destruction and permeation, centered on the region of the vestibular aqueduct

(Figure 4). Mean (SD) tumor diameter was 2.2 cm (1.6 cm) (range, 0.5-5.2 cm).

Ears Without Otic Capsule Invasion

Clinical Findings. Thirty-one ears (11 right, 20 left) among 30 patients (14 male, 16 female) were affected by ELSTs that did not invade the otic capsule. One patient had bilateral ELSTs that were not associated with otic capsule invasion. Mean (SD) age at audiovestibular symptom onset was 32 (13.1) years (range, 11-63 years). Overall, mean (SD) follow-up was 95.4 (56.2) months (range, 3-192 months).

Twenty-seven of the 31 ears (87%) without otic capsule invasion had SNHL (4 ears had normal hearing). SNHL in these ears was mild to moderate in 15 ears (56%) and severe to profound in 12 ears (44%). The hearing loss in the 27 patients with SNHL occurred either suddenly (14 ears; 52%) or gradually (13 ears; 48%) over months to years. Additional audiovestibular findings included tinnitus (23 ears; 74%), vertigo (21 patients; 70%), aural fullness (10 ears; 32%), aural pain (3 ears; 10%), and facial nerve weakness (1 ear; 3%). Tinnitus was continuous in 12 affected ears (52%) and intermittent in 11 (48%). Vertigo was continuous in 4 affected patients (19%) and intermit-

tent in 17 (81%). Aural fullness was continuous in 2 affected ears (20%) and intermittent in 8 (80%). Aural pain was continuous in 3 affected ears (100%).

Imaging. Thirty (97%) of 31 ELSTs without otic capsule invasion had imaging features consistent with an ELST. The mean (SD) tumor diameter for these tumors was 1.2 cm (0.7 cm) (range, 0.2-2.6 cm), which was smaller (analysis of variance; $P = .01$) than those ELSTs that invaded the otic capsule (mean (SD) diameter 2.2 cm [1.6 cm]; range, 0.5-5.2 cm). One ELST (3%) was not visible on MRI or CT imaging, but was suspected because of intralabyrinthine hemorrhage (visible on T1-weighted MRI) that corresponded with sudden SNHL, vertigo, and tinnitus. Surgical exploration revealed a small ELST (2 mm) that was resected.

Hyperintense signal on precontrast T1- and fluid attenuated inversion recovery-weighted MRI, indicative of intralabyrinthine hemorrhage (FIGURE 5), was seen in 11 of the 14 ears (79%) in which sudden SNHL was identified clinically (χ^2 test; $P < .001$). In the 13 ears without otic capsule invasion in which SNHL occurred gradually, there was no evidence of intralabyrinthine hemorrhage (on precontrast T1-weighted or fluid attenuated inversion recovery MRI; FIGURE 6). Similarly, none of the 4 patients without otic capsule invasion and normal hearing had evidence of intralabyrinthine hemorrhage. There was no correlation between tumor size and the presence of intralabyrinthine hemorrhage (univariate analysis of variance; $P = .13$) among the ELSTs without otic capsule invasion.

COMMENT

ELSTs in VHL Disease

VHL has an incidence of 1 in 39 000 individuals.⁶ It is an autosomal dominant neoplasia syndrome that is the result of a germline mutation or deletion of the VHL tumor suppressor gene on the short arm of chromosome 3.⁷⁻⁹ VHL is associated with variable penetrance and heterogeneous clinical findings. Affected individuals often develop benign and

malignant visceral and central nervous system lesions.^{8,10} Visceral manifestations include renal cysts and carcinomas, pheochromocytomas, pancreatic cysts and neuroendocrine tumors, as well as reproductive adnexal organ cystadenomas.^{8,11,12} Central nervous system manifestations include retinal, cerebellar, spinal cord, and brainstem hemangioblastomas, as well as ELSTs.^{8,10}

ELSTs were clinically established as part of the VHL syndrome by Manski et al³ and confirmed by genetic analyses of Vortmeyer et al.^{13,14} While these tumors rarely occur in the general population, they are found frequently in patients with VHL by MRI or CT imaging with an estimated incidence of 11% to 16%.^{3,4,8,15} VHL is the only condition identified that is associated with bilateral ELSTs.^{3,4} While 9% of patients in this study had bilateral ELSTs, previous reports have suggested that bilateral tumors may occur in as many as 15% to 30% of patients with VHL with ELSTs.^{3,16} These previous estimates may be higher in part because they were based on summaries of case reports or isolated smaller series.

All patients in this series developed audiovestibular symptoms. Analogous with a pathophysiologic process within the endolymphatic system, most patients presented with a triad of findings frequently associated with Menière disease that includes hearing loss, tinnitus, and vertigo (Table).^{1,4,17} This often led to a referral diagnosis of Menière disease before discovery of an ELST. Consistent with previous reports that describe a 90% incidence of either gradual or sudden SNHL in patients with ELST,^{3,4,18} the most common ELST-associated clinical finding in this series was hearing loss. SNHL occurred in 31 patients (89%) or 34 of the affected ears (89%) and was frequently moderate or profound (Figure 2). Other less frequent ELST-associated findings included aural fullness, aural pain, facial nerve weakness, and aural pain and facial nerve weakness combined (Table).

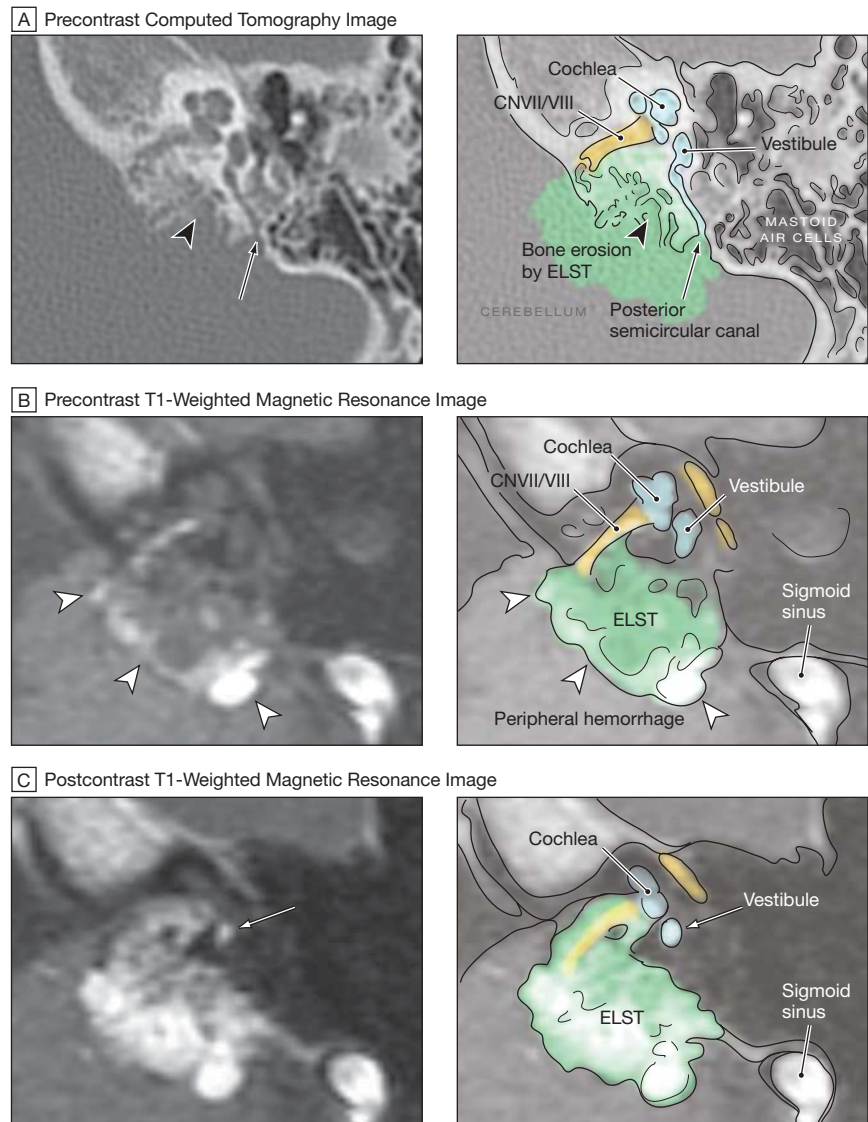
Consistent with the anatomic origin and known progressive erosive nature of ELSTs, otic capsule invasion occurred

with tumors that were significantly larger than those that did not invade the otic capsule. Analysis of tumor size and its relationship to the presence of SNHL and audiovestibular symptomatology revealed no association (Figure 3). The lack of correlation between tumor size and SNHL, as well as the presence of SNHL

and vestibulopathy in patients without otic capsule invasion, supports the hypothesis that mechanisms other than otic capsule destruction by tumor expansion underlie the audiovestibular morbidity linked to ELSTs.

While we did not find a link between tumor size and SNHL, Manski et

Figure 4. Large Endolymphatic Sac Tumor With Invasion of the Otic Capsule Associated With Profound Hearing Loss



Invasion of the otic capsule by a large endolymphatic sac tumor (ELST) in a 38-year-old patient with von Hippel-Lindau disease and profound hearing loss. A, Axial precontrast computed tomography (CT) image demonstrates extensive temporal bone destruction (black arrowhead) with erosion into the otic capsule at the posterior semicircular canal (black arrow). B, Axial precontrast T1-weighted magnetic resonance image (MRI) demonstrates isointense tumor associated with hyperintense peripheral hemorrhage (white arrowheads). C, Axial postcontrast T1-weighted MRI demonstrates enhancement of the bulk of the ELST, which directly extends into the labyrinth (white arrow). CN indicates cranial nerve.

al³ reported that increased tumor size was associated with loss of functional hearing in 13 patients with VHL with 15 ELSTs. The most likely reason for this difference is related to the timing of ELST discovery. Until Manski et al³

made the definitive clinical association of ELSTs in VHL, patients with VHL were not routinely screened for ELSTs. Thus, detection of ELSTs, including those in the series of Manski et al,³ were delayed and patients frequently had large

tumors that were associated with long-standing hearing loss at diagnosis. Improvements in imaging resolution, as well as the development of targeted clinical and imaging screening protocols, now permit early detection of very small ELSTs and their effects on the inner ear. The results of these studies, as described in this series of patients, reveal that audiovestibular morbidity occurs frequently with small ELSTs (2-3 mm in diameter; Figure 3).

The detection of smaller ELSTs and their associated effects (ie, intralabyrinthine hemorrhage) give insight into the mechanism of the previously reported high incidence of audiovestibular dysfunction (including unexplained sudden hearing loss) in patients with VHL without radiographic evidence of ELST.^{3,4} Using serial high-resolution MRI and CT imaging with specific sequences to evaluate the inner ear, we detected several small tumors (<5 mm diameter) and found that a large number of patients in this study (29%) had intralabyrinthine hemorrhage that corresponded with sudden SNHL that may not have been detected using lower-resolution imaging or imaging that was not clinically correlated with audiovestibular dysfunction (ie, before the inclusion of ELSTs in the VHL syndrome). This point is underscored by the detection of a small ELST by the presence of intralabyrinthine hemorrhage on MRI and confirmed surgically to be in the vestibular aqueduct.

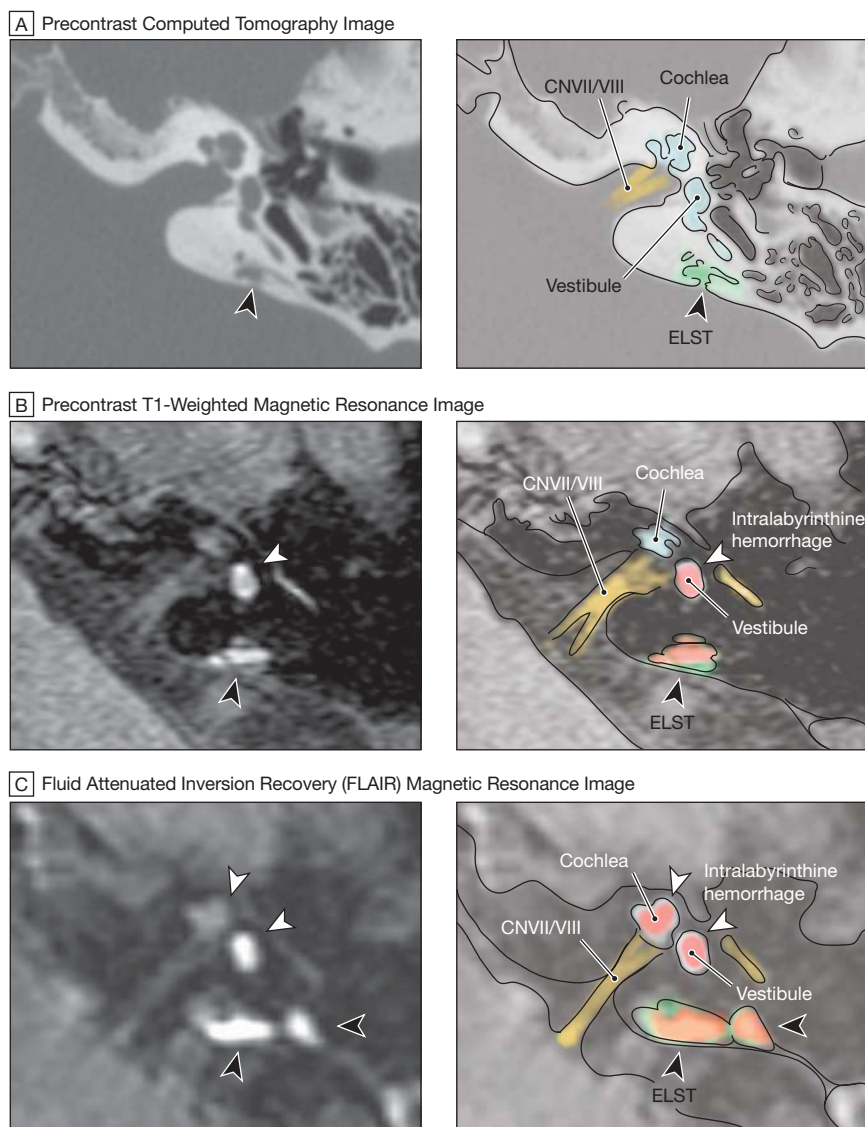
Mechanisms of Hearing Loss

Based on the relationship between the imaging and clinical findings in these patients, 3 distinct mechanisms (either alone or in combination) may account for the audiovestibular morbidity associated with ELSTs. These include direct invasion of the otic capsule by tumor, intralabyrinthine hemorrhage, and endolymphatic hydrops.

Otic Capsule Invasion by Tumor

Because otic capsule destruction is a well-described mechanism of hearing loss and vestibulopathy and because

Figure 5. Small Endolymphatic Sac Tumor With Intralabyrinthine Hemorrhage Associated With Sudden Hearing Loss



A small endolymphatic sac tumor (ELST) that did not involve the otic capsule in a 68-year-old patient with von Hippel-Lindau disease and sudden hearing loss (normal to profound hearing loss on audiogram) resulting from intralabyrinthine hemorrhage. A, Axial computed tomography (CT) image demonstrates erosion of the posterior temporal bone by an ELST (black arrowhead) located at the vestibular aqueduct with no extension anteriorly toward the otic capsule. Axial magnetic resonance images (MRIs) of the temporal bone, B (T1-weighted) and C (FLAIR), reveal a hyperintense signal (black arrowheads) in the location of the tumor. Evidence of intralabyrinthine hemorrhage is seen in the vestibule and in the cochlea (white arrowheads). The morphology of the labyrinth of the inner ear is normal in all images. CN indicates cranial nerve.

previous descriptions of ELST-associated hearing loss and vestibulopathy occurred most often in the context of large tumors, previous reports emphasized that hearing loss associated with ELSTs was the result of direct invasion of the otic capsule by tumor.^{1,4,19,20} Similarly, this report demonstrates that larger tumor size is associated with radiographic evidence of otic capsule invasion. Although it is possible that diagnostic imaging could miss detection of histologic invasion of the otic capsule, previous reports of small ELSTs with imaging evidence of an intact otic capsule did not have histologic evidence of otic capsule invasion.^{2,5,16} When an ELST directly erodes into the inner ear, it destroys the membranous labyrinth and disrupts endolymphatic flow, causing hearing loss and vestibulopathy (Figure 4).

Intralabyrinthine Hemorrhage

The results described in this study indicate that acute intralabyrinthine hemorrhage by an ELST explains the frequent occurrence of irreversible, sudden, and significant hearing loss that occurs in patients with ELSTs (Figure 5).²⁻⁴ This is supported by the presence of intralabyrinthine hemorrhage on MRI that was associated with sudden hearing loss in 77% of ears with SNHL and no evidence of otic capsule invasion (Figure 2). These findings are further underscored by a previously reported autopsy case demonstrating hemosiderin in the inner ear of a patient with VHL and sudden hearing loss associated with a microscopic ELST,² a patient with ELST with sudden hearing loss coinciding with MRI evidence of intralabyrinthine hemorrhage,²¹ and ELSTs from patients with sudden SNHL (without otic capsule invasion) who demonstrate intratumoral hemosiderin and hemorrhage.⁵ The irreversibility of symptoms (particularly hearing loss) in such patients may be the result of neuronal degeneration caused by hemorrhage, secondary inflammation, or both.²

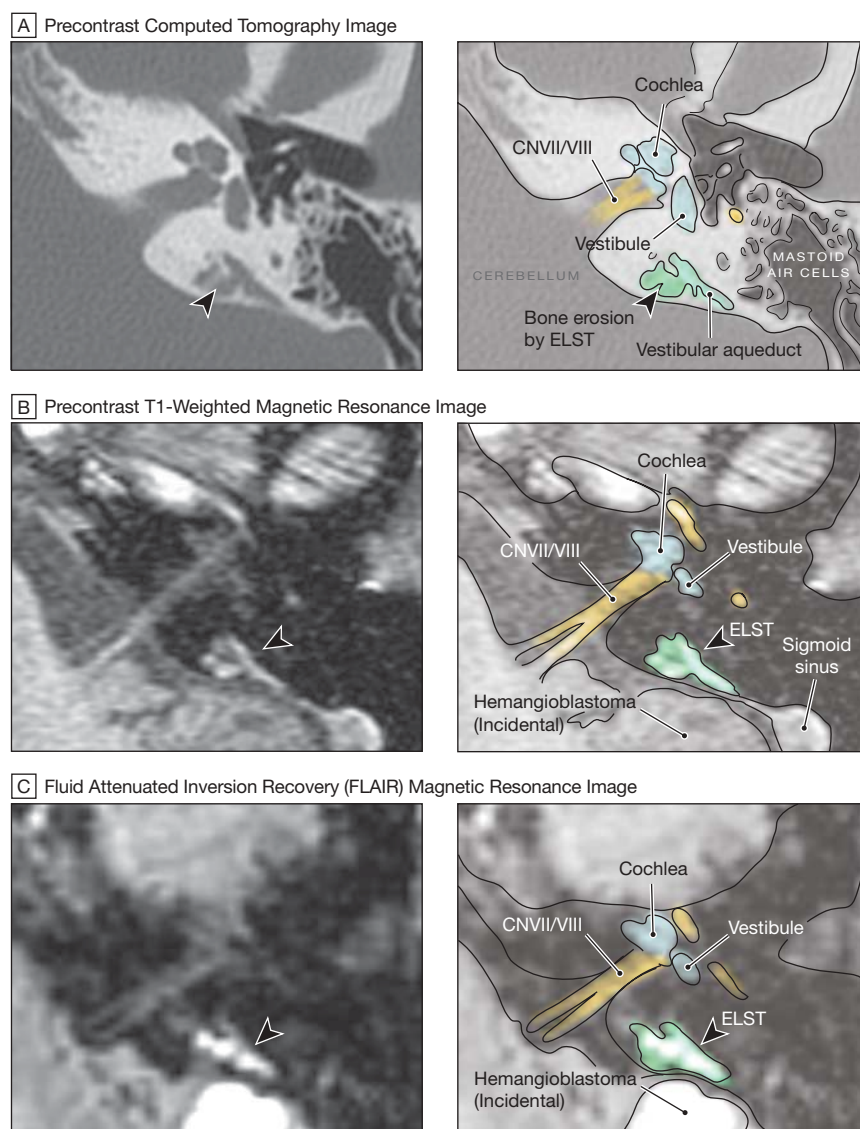
Endolymphatic Hydrops

The remaining patients presented with a clinical syndrome (gradual hearing loss,

tinnitus, and vertigo) typical of Ménière disease, suggesting that endolymphatic hydrops develops in patients with ELSTs (Figure 2; Table).⁴ In support of this, a patient with VHL and anterem symptoms consistent with Ménière disease, including tinnitus, vertigo, and

hearing loss was found to have endolymphatic hydrops and a microscopic ELST on postmortem histopathology.² Blockage of endolymphatic sac resorption of endolymph, inflammation in response to hemorrhage, or excessive production of fluid by the tumor may

Figure 6. Small Endolymphatic Sac Tumor Associated With Gradual Hearing Loss



A small endolymphatic sac tumor (ELST) with no evidence of intralabyrinthine hemorrhage or otic capsule invasion in a 31-year-old patient with von Hippel-Lindau disease. The patient experienced gradual hearing loss (from normal hearing to moderate/severe loss on audiogram) over a 5-year period, intermittent vertigo, and tinnitus. A, Axial precontrast computed tomography (CT) image demonstrates erosion of the posterior temporal bone by an ELST (black arrowhead) located at the vestibular aqueduct. Axial magnetic resonance images of the temporal bone, B (T1-weighted) and C (FLAIR), reveal a hyperintense signal (black arrowheads) in the location of the tumor. No evidence of intralabyrinthine hemorrhage is present as demonstrated by the normal hypointense signal seen in the vestibule and cochlea in both B and C. CN indicates cranial nerve.

individually or in combination cause hydrops.^{4,22,23} Production of peritumoral fluid by ELSTs is analogous to the formation of peritumoral edema and cysts that are frequently associated with central nervous system hemangioblastomas^{24,25} and visceral tumors in VHL.^{8,23,26}

Implications for Surveillance and Treatment

Previously, the management of ELSTs (particularly tumors that were small and asymptomatic) has been conservative because they have an uncertain natural history and are not considered malignant or fast growing.^{3,4} This study demonstrates that audiovestibular morbidity is frequently associated with small tumors (those not invading the otic capsule) and occurs by mechanisms that include intralabyrinthine hemorrhage and hydrops. Since significant audiovestibular dysfunction, including deafness, can occur suddenly in a manner that is not related to tumor size, early surgical intervention may be warranted. While this study does not address the effectiveness of surgical resection, several small operative series indicate that complete resection of ELSTs can be curative, can alleviate vestibular symptomatology, and can be performed with hearing preservation and minimal morbidity.^{5,16,19,20} Therefore, in patients with hearing and imaging evidence of an ELST, surgery may be considered after weighing its potential risks to prevent neurologic worsening or amelioration of symptoms. To intervene early, prompt diagnosis based on clinical and imaging findings is necessary. Thus, serial clinical evaluations and high-resolution MRI and CT imaging to detect small ELSTs or intralabyrinthine

hemorrhage are warranted in patients with VHL.

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Acquisition of data: Butman, Kim, Baggenstos, Ammerman, Patsalides, Patronas.

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Drafting of the manuscript: Butman, Lonser.

Critical revision of the manuscript for important intellectual content: Butman, Kim, Oldfield, Lonser.

Statistical analysis: Dambrosia.

Administrative, technical, or material support: Butman, Kim, Oldfield, Lonser.

Study supervision: Butman, Kim, Oldfield, Lonser.

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REFERENCES

- Heffner DK. Low-grade adenocarcinoma of probable endolymphatic sac origin: a clinicopathologic study of 20 cases. *Cancer*. 1989;64(11):2292-2302.
- Lonser RR, Kim HJ, Butman JA, Vortmeyer AO, Choo D, Oldfield E. Tumors of the endolymphatic sac in von Hippel-Lindau disease. *N Engl J Med*. 2004;350(24):2481-2486.
- Manski TJ, Heffner DK, Glenn GM, et al. Endolymphatic sac tumors: a source of morbid hearing loss in von Hippel-Lindau disease. *JAMA*. 1997;277(18):1461-1466.
- Choo D, Shotland L, Mastroianni M, et al. Endolymphatic sac tumors in von Hippel-Lindau disease. *J Neurosurg*. 2004;100(3):480-487.
- Kim HJ, Butman JA, Brewer C, et al. Tumors of the endolymphatic sac in patients with von Hippel-Lindau disease. *J Neurosurg*. 2005;102(3):503-512.
- Neumann HP, Wiestler OD. Clustering of features of von Hippel-Lindau syndrome. *Lancet*. 1991;337(8749):1052-1054.
- Latif F, Tory K, Gnarr J, et al. Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*. 1993;260(5112):1317-1320.
- Lonser RR, Glenn GM, Walther M, et al. von Hippel-Lindau disease. *Lancet*. 2003;361(9374):2059-2067.
- Wait SD, Vortmeyer AO, Lonser RR, et al. Somatic mutations in VHL germline deletion kindred correlate with mild phenotype. *Ann Neurol*. 2004;55(2):236-240.

10. Richard S, Campello C, Taillandier L, Parker F, Resche F. Haemangioblastoma of the central nervous system in von Hippel-Lindau disease: French VHL Study Group. *J Intern Med*. 1998;243(6):547-553.

11. Linehan WM, Lerman MI, Zbar B. Identification of the von Hippel-Lindau (VHL) gene: its role in renal cancer. *JAMA*. 1995;273(7):564-570.

12. Libutti SK, Choyke PL, Alexander HR, et al. Clinical and genetic analysis of patients with pancreatic neuroendocrine tumors associated with von Hippel-Lindau disease. *Surgery*. 2000;128(6):1022-1027.

13. Vortmeyer AO, Choo D, Pack SD, Oldfield E, von Zhuang Z. Hippel-Lindau disease gene alterations associated with endolymphatic sac tumor. *J Natl Cancer Inst*. 1997;89(13):970-972.

14. Vortmeyer AO, Choo D, Pack S, Oldfield E, Zhuang Z. VHL gene inactivation in an endolymphatic sac tumor associated with von Hippel-Lindau disease. *Neurology*. 2000;55(3):460.

15. Megeerian CA, McKenna MJ, Nuss RC, et al. Endolymphatic sac tumors. *Laryngoscope*. 1995;105(8, pt 1):801-808.

16. Megeerian CA, Haynes DS, Poe DS, Choo DI, Keriakas TJ, Glasscock ME III. Hearing preservation surgery for small endolymphatic sac tumors in patients with von Hippel-Lindau syndrome. *Otol Neurotol*. 2002;23(3):378-387.

17. Schuknecht HF, Belal AA. The utriculo-endolymphatic valve: its functional significance. *J Laryngol Otol*. 1975;89(10):985-996.

18. Thomassin JM, Roche PH, Braccini F, Epron JP, Pellet W. Endolymphatic sac tumors [published in French]. *Ann Otolaryngol Chir Cervicofac*. 2000;117(5):274-280.

19. Hansen MR, Luxford WM. Surgical outcomes in patients with endolymphatic sac tumors. *Laryngoscope*. 2004;114(8):1470-1474.

20. Rodrigues S, Fagan P, Turner J. Endolymphatic sac tumors. *Otol Neurotol*. 2004;25(4):599-603.

21. Gaeta M, Blandino A, Minutoli F, Pandolfo I. Sudden unilateral deafness with endolymphatic sac adenocarcinoma: MRI. *Neuroradiology*. 1999;41(10):799-801.

22. Lonser RR, Vortmeyer AO, Butman JA, et al. Edema is a precursor to central nervous system peritumoral cyst formation. *Ann Neurol*. 2005;58(3):392-399.

23. Walther MM, Lubensky IA, Venzon D, Zbar B, Linehan WM. Prevalence of microscopic lesions in grossly normal renal parenchyma from patients with von Hippel-Lindau disease, sporadic renal cell carcinoma and no renal disease: clinical implications. *J Urol*. 1995;154(6):2010-2014.

24. Lonser RR, Weil RJ, Wanebo JE, DeVroom HL, Oldfield EH. Surgical management of spinal cord hemangioblastomas in patients with von Hippel-Lindau disease. *J Neurosurg*. 2003;98(1):106-116.

25. Wanebo JE, Lonser RR, Glenn GM, Oldfield EH. The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. *J Neurosurg*. 2003;98(1):82-94.

26. Libutti SK, Choyke PL, Bartlett DL, et al. Pancreatic neuroendocrine tumors associated with von Hippel-Lindau disease: diagnostic and management recommendations. *Surgery*. 1998;124(6):1153-1159.