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The vestibular aqueduct: site of origin of endolymphatic sac tumors

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Abstract

Object—Although endolymphatic sac tumors (ELSTs) frequently destroy the posterior petrous bone and cause hearing loss, the anatomical origin of these neoplasms is unknown. To determine the precise topographic origin of ELSTs, the authors analyzed the imaging, operative, and pathological findings in patients with von Hippel–Lindau disease (VHL) and ELSTs.

Methods—Consecutive VHL patients with small (≤ 1.5 cm) ELSTs who underwent resection at the National Institutes of Health were included. Clinical, imaging, operative, and pathological findings were analyzed.

Results—Ten consecutive VHL patients (6 male and 4 female) with 10 small ELSTs (≤ 1.5 cm; 9 left, 1 right) were included. Serial imaging captured the development of 6 ELSTs and revealed that they originated within the intraosseous (vestibular aqueduct) portion of the endolymphatic duct/sac system. Imaging just before surgery demonstrated that the epicenters of 9 ELSTs (1 ELST was not visible on preoperative imaging) were in the vestibular aqueduct. Inspection during surgery established that all 10 ELSTs were limited to the intraosseous endolymphatic duct/sac and the immediately surrounding region. Histological analysis confirmed tumor within the intraosseous portion (vestibular aqueduct) of the endolymphatic duct/sac in all 10 patients.

Conclusions—ELSTs originate from endolymphatic epithelium within the vestibular aqueduct. High-resolution imaging through the region of the vestibular aqueduct is essential for diagnosis. Surgical exploration of the endolymphatic duct and sac is required for complete resection.

Keywords

anatomy; endolymphatic sac tumor; origin; pathology; vestibular aqueduct

Endolymphatic sac tumors were first established as a pathological entity by Heffner in 1989³ after he described the unique anatomical and histological features in 20 benign papillary-cystic neoplasms in the region of the posterior temporal bone. Based on anatomical estimations derived from the approximate epicenter of large tumors, Heffner concluded that the “probable”

region of neoplastic origin was the posterior-medial face of the petrous temporal bone. Because the extraosseous portion of the endolymphatic sac is located in this anatomical region and because the tumors analyzed had histological similarities to endolymphatic epithelium, he attributed the origin of these neoplasms to the endolymphatic sac. Despite these critical insights and findings, Heffner felt that the precise “region of origin is limited to a small size” but was not able to define this site because of the large and extensive involvement of the ELSTs available for his evaluation.

Although ELSTs can occur sporadically, they are frequently associated with VHL disease.⁷ Because of the association of ELSTs with VHL disease, investigators have performed serial imaging studies—MR imaging and CT of the temporal bones—using high-resolution protocols that can capture the development of the tumors in these patients.^{4,6} These findings from these imaging studies, when correlated with operative and pathological findings, provide direct insight into the precise origin of these tumors. Because accurate determination of the site of origin of ELSTs has important clinical and pathological implications, we analyzed the clinical, imaging, operative, and pathological findings in cases in which ELSTs developed in patients with VHL disease, the development was captured on serial imaging, and the ELSTs were resected.

Clinical Materials and Methods

Patient Population and Clinical Evaluation

Consecutive patients with VHL disease who were evaluated at the National Institutes of Health, had small ELSTs (≤ 1.5 cm in diameter), and underwent resection between July 2001 and the end of December 2006 were included.

Patients underwent serial neurotologic examinations at intervals of approximately 6–12 months. Data from inpatient charts, clinic notes, audiograms, operative reports, and pathological findings were analyzed.

Imaging Evaluation

Patients underwent serial (pre- and postcontrast), high-resolution, T1-weighted, T2-weighted, and FLAIR MR-imaging. They also underwent serial, high-resolution CT of the temporal bones. Tumor size was determined by the largest tumor diameter in any single plane measured on MR images.

Operative Evaluation

To resect small ELSTs (≤ 1.5 cm), we use an RLPP approach.⁴ This approach permits direct access and visualization of the intra- and extraosseous endolymphatic duct/sac system. Specimens including gross tumor, the intraosseous (within the vestibular aqueduct) endolymphatic duct/sac, and the extraosseous endolymphatic sac (within posterior fossa dura) were removed separately and separately submitted for site-specific histopathological analysis.

Pathological Evaluation

Surgically resected tissues labeled “tumor,” “extraosseous portion of endolymphatic sac,” or “intraosseous portion of endolymphatic sac” were separately received in the pathology department, separately processed, and individually analyzed. Histopathological detection of pathological changes was followed by immunohistochemical analysis of well-established epitopes of interest including MAK6 and CD31.²

Results

Patient Characteristics

Included in this study were 10 consecutive patients with VHL disease (6 male and 4 female patients) who underwent resection of 10 (9 left, 1 right) small ELSTs (≤ 1.5 cm in diameter). Their mean age ($\pm$ standard deviation) at the time of tumor resection was 39.0 ± 7.4 years (range, 28–50 years). Mean duration of follow-up after surgery was 32.8 ± 13.4 months (range 3–48 months). Overall, the duration of follow-up was 81.9 ± 64.6 months (range 4.9–143.3 months). The mean tumor diameter at the time of resection was 0.8 ± 0.5 cm (range 0.2–1.5 cm). All patients had audiovestibular symptoms at the time of surgery, including hearing loss (10 [100%] of 10 patients), vertigo (8 [80%] of 10 patients), tinnitus (8 [80%] of 10 patients), and/or aural fullness (5 [50%] of 10 patients).

Tumor Origin

Imaging Findings—Nine of 10 patients had imaging evidence of an ELST at the time of surgery. Magnetic resonance imaging in these patients revealed an enhancing tumor mass centered in the vestibular aqueduct and CT demonstrated osseous erosion in the region immediately surrounding the ELST (Figs. 1 and 2). The development of an ELST was captured in neuroimaging studies in 6 cases (Fig. 2). Findings from these cases revealed that an enhancing ELST originated in the portion of the endolymphatic system contained within the osseous vestibular aqueduct. One patient had no MR imaging or CT evidence of a tumor mass but had evidence of intralabyrinthine hemorrhage on T1-weighted and FLAIR MR imaging. Surgical exploration revealed a 0.2-cm tumor confined to the endolymphatic duct.

Operative Findings—The RLPP provided excellent exposure to the ELST, the osseous endolymphatic system (distal duct and proximal sac) within the vestibular aqueduct, and the extraosseous endolymphatic system (distal sac) contained within the dura mater of the anterior region of the posterior fossa. The direct exposure permitted selective resection of each of these structures for separate anatomical histopathological analysis. Gross tumor was identified within the vestibular aqueduct and the immediately surrounding temporal bone in all cases. While the extraosseous portion of the endolymphatic sac (anterior posterior fossa dura) appeared vascularized relative to other distant dural regions in all cases, there was no gross evidence of tumor seen at surgery.

Pathological Findings—In all 10 cases, the material that was resected from the intraosseous portion of the endolymphatic sac and separately submitted contained ELST upon histological examination. In 8 cases, separately submitted samples of the extraosseous portion of the endolymphatic sac were tumor-free upon histological examination, and lack of tumor was confirmed after serial sectioning of the specimens at 50- μ m intervals. In 2 other cases, microscopic amounts of papillary-cystic tumor were observed to extend into the extraosseous part of the endolymphatic sac. Overall, all 10 tumors were located within the intraosseous portion of the endolymphatic sac, 8 of them exclusively.

Discussion

Endolymphatic Sac and Duct Anatomy

The endolymphatic sac and duct are part of the membranous labyrinth of the inner ear (Fig. 3).⁵ The endolymphatic duct is connected to the membranous labyrinth of the inner ear by the saccular and utricular ducts. These ducts are directly connected to the saccule and utricle, respectively, by bidirectional valves. The saccular and utricular ducts form the sinus of the endolymphatic duct, which is located in the bony vestibule. The sinus of the endolymphatic duct tapers and becomes the isthmus of the endolymphatic duct as it enters the bony vestibular

aqueduct. The isthmus of the endolymphatic duct connects to the intraosseous portion (within the vestibular aqueduct) of the endolymphatic sac. Distally, the extraosseous portion of the endolymphatic sac begins as the sac exits the aperture of the vestibular aqueduct. The extraosseous portion of the sac resides between the leaves of the posterior fossa dura mater on the posterior wall of the petrous ridge.

Endolymphatic Sac Tumors

Endolymphatic sac tumors are associated with erosion of the posterior petrous bone. These tumors occur sporadically or in the context of the autosomal dominant neoplasia syndrome, VHL disease (ELST incidence of 15%).^{1,7} In patients with VHL disease, bilateral ELSTs can be frequently found (occurring in 30% of patients with VHL who have an ELST).⁹ Endolymphatic sac tumors are locally invasive (invading the temporal bone), and as a result, are frequently associated with significant audiovestibular morbidity, including deafness, tinnitus, and vertigo.^{1,7-9} Because surgical resection is curative and the onset of audiovestibular morbidity is unpredictable and not related to tumor size, early surgery has been recommended to reduce the morbidity related to these neoplasms.^{4,6,8}

Heffner's classification of ELSTs as "low-grade adenocarcinoma of probable endolymphatic sac origin" left the exact anatomical and cellular origin unclear.³ The imaging, operative and histopathological data from the patients in this study indicates that ELSTs arise from the osseous portion (vestibular aqueduct) of the endolymphatic duct/sac system. Imaging demonstrating development of these tumors in the vestibular aqueduct and the fact that the epicenter of larger tumors is at this site provide support for this anatomical origin. Operative findings, consistent with the imaging evidence, lend further support to this topographic origin of ELSTs. Moreover, similar to the findings in our series of small ELSTs showing preferential temporal bone erosion, all the large ELSTs in Heffner's original series demonstrated bone destruction,³ which would not be expected to occur so frequently if the tumors originated outside of bone. Finally, separate site-specific histopathological analysis of the osseous (vestibular aqueduct) endolymphatic duct/sac system and extraosseous endolymphatic duct/sac system (posterior fossa dura mater including the sac) provided confirmation that these tumors arise in the region of the vestibular aqueduct.

Clinical Implications

Because early surgical intervention can reduce the morbidity associated with ELSTs and because these tumors cause significant audiovestibular morbidity when they are small (< 2 mm), understanding the precise topographical location of these lesions provides critical insights that aid in their diagnosis and successful surgical treatment. High-resolution MR imaging and CT directed to the region of the vestibular aqueduct (in addition to the extraosseous portion of the endolymphatic sac) may reduce the possibility of missing a small ELST in patients with audiovestibular symptomatology. This is particularly important in patients with VHL disease and audiovestibular dysfunction in whom an ELST may be missed because MR imaging and CT studies incompletely evaluated the region of the vestibular aqueduct. Furthermore, because ELSTs arise in the osseous (vestibular aqueduct) portion of the endolymphatic duct/sac system, complete surgical resection of these tumors requires exploration and removal of tumor from the osseous vestibular aqueduct and possibly the extraosseous portion of the endolymphatic sac.

Developmental Implications

Previous studies of tissues from patients with VHL disease revealed multifocal, VHL-deficient epithelial cell proliferations throughout the endolymphatic duct and sac that are likely to represent potential precursor structures for the development of frank tumor.² At the same time, the abundance of precursor structures detected in the endolymphatic sac and duct in a patient

without an ELST at autopsy suggested that most precursor structures do not develop into frank tumor during the lifetime of an individual patient.¹⁰ While evidence is emerging in other VHL target sites that tumor progression is associated with activation of separate proteins, which are undetectable in potential precursor lesions, no “activating” mechanism is currently known that would differentiate early tumor from precursor state in the endolymphatic sac or duct. To obtain definitive insight into the site of origin of ELSTs, we therefore focused on a group of patients with tumors that were small enough to be completely confined to their site of origin, but large enough to be grossly visible and qualify as an independent tumor. By studying this group of patients in detail we consistently observed tumorigenesis to occur in the intraosseous portion of the endolymphatic sac and duct. It remains to be clarified whether the progression from microscopic precursor into frank tumor is the result of specific molecular signaling and whether specific environmental conditions within the intraosseous portion of endolymphatic sac/duct may facilitate such events.

Conclusions

Serial focused screening and evaluation of at-risk patients with VHL disease captured the development of small ELSTs, and resection combined with site-specific histological analyses revealed that tumorigenesis occurs in the vestibular aqueduct (intraosseous) portion of the endolymphatic sac/duct system. This site specificity indicates that biological or environmental differences in this anatomical region of the endolymphatic system predispose endolymphatic sac/duct tissues for tumor development. Understanding that these tumors develop in the vestibular aqueduct will enhance imaging discovery and the effectiveness of surgical treatment.

Acknowledgments

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Abbreviations in this paper

CT	computed tomography
ELST	endolymphatic sac tumor
MR	magnetic resonance
RLPP	retrolabyrinthine posterior petrosectomy
VHL	von Hippel–Lindau

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Fig. 1.

Characteristic imaging and histological findings from a 40-year-old patient with VHL disease who had a right-sided ELST and preoperative symptomatology that included right-sided hearing loss, tinnitus, and vertigo. A: Axial, T1-weighted, enhanced MR image demonstrating a small (3-mm) enhancing lesion (*arrowhead*) within the right vestibular aqueduct (external aperture of vestibular aqueduct, *arrow*). B: Corresponding axial unenhanced CT image demonstrating osseous erosion by tumor (*arrowhead*) within the proximal vestibular aqueduct (external aperture of vestibular aqueduct, *arrowhead*). Consistent with imaging findings, a small ELST was identified within the vestibular aqueduct. C: Hematoxylin and eosin staining demonstrates a papillary-cystic ELST. Original magnification $\times 20$. D: Immunohistochemical staining for CD34 antigen (*dark staining*) demonstrates the intense vascularization characteristic of ELSTs. Original magnification $\times 20$.

Fig. 2.

Serial imaging and histological findings in a 38-year-old patient with VHL disease that demonstrate the development of a left-sided ELST within the vestibular aqueduct. The patient presented in 2000 with acute onset of left-sided tinnitus. A: Axial, T1-weighted, enhanced MR imaging did not demonstrate evidence of an ELST. In 2002, the patient presented with worsening tinnitus and acute left-sided hearing loss. B: Axial, T1-weighted, enhanced MR imaging at that time demonstrated an enhancing tumor (*arrow*) within the proximal vestibular aqueduct. C: Corresponding axial, unenhanced CT imaging demonstrated tumor-associated erosion in the vestibular aqueduct (*arrowhead*). Consistent with imaging findings, a small ELST was identified within the vestibular aqueduct. D: Hematoxylin and eosin staining demonstrates a papillary-cystic ELST. Original magnification $\times 20$.

Fig. 3.

Schematic illustration detailing the anatomy of the endolymphatic system and its relationship to surrounding petrous bone structure. The endolymphatic sac and duct are part of the membranous labyrinth of the inner ear. The endolymphatic duct is connected to the membranous labyrinth of the inner ear by the saccular and utricular ducts. The saccular and utricular ducts form the sinus of the endolymphatic duct. The sinus of the endolymphatic duct tapers and becomes the isthmus of the endolymphatic duct as it enters the bony vestibular aqueduct. The isthmus of the endolymphatic duct connects to the intraosseous portion (within the vestibular aqueduct) of the endolymphatic sac. Endolymphatic sac tumors arise from the endolymphatic epithelium of the endolymphatic duct and sac with the vestibular aqueduct (osseous portion, *striped area*). Distally, the extraosseous portion of the endolymphatic sac begins as the sac exits the aperture of the vestibular aqueduct. The extraosseous portion of the sac resides between the leaves of the posterior fossa dura mater on the posterior wall of the petrous ridge.