Endolymphatic sac tumor demonstrated by intralabyrinthine hemorrhage

Case report

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Endolymphatic sac tumors (ELSTs) are locally invasive neoplasms that arise in the posterior petrous bone and are associated with von Hippel–Lindau (VHL) disease. These tumors cause symptoms even when microscopic in size (below the threshold for detectability on imaging studies) and can lead to symptoms such as hearing loss, tinnitus, vertigo, and facial nerve dysfunction. While the mechanisms of audiovestibular dysfunction in patients harboring ELSTs are incompletely understood, they have critical implications for management. The authors present the case of a 33-year-old man with VHL disease and a 10-year history of progressive tinnitus, vertigo, and left-sided hearing loss. Serial T1-weighted magnetic resonance (MR) imaging and computed tomography scans revealed no evidence of tumor, but fluid attenuated inversion recovery (FLAIR) MR imaging sequences obtained after hearing loss demonstrated evidence of left intralabyrinthine hemorrhage. On the basis of progressive disabling audiovestibular dysfunction (tinnitus and vertigo), FLAIR imaging findings, and VHL disease status, the patient underwent surgical exploration of the posterior petrous region, and a small (2-mm) ELST was identified and completely resected. Postoperatively, the patient had improvement of the tinnitus and vertigo. Intralabyrinthine hemorrhage may be an early and the only neuroimaging sign of an ELST in patients with VHL disease and audiovestibular dysfunction. These findings support tumor-associated hemorrhage as a mechanism underlying the audiovestibular dysfunction associated with ELSTs.

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KEY WORDS • endolymphatic sac tumor • hemorrhage • mechanism • von Hippel–Lindau disease

Abbreviations used in this paper: CT = computed tomography; ELST = endolymphatic sac tumor; FLAIR = fluid attenuated inversion recovery; MR = magnetic resonance; VHL = von Hippel–Lindau.

Endolymphatic sac tumors are histologically benign but invasive tumors that arise from the endolymphatic duct or sac in the region of the posterior petrous bone.3,10 Because of their invasive nature, ELSTs frequently cause hearing loss (often sudden and significant), tinnitus, vertigo, aural fullness, and facial nerve dysfunction.12 Although they can occur sporadically, ELSTs are frequently associated with VHL disease (Online Mendelian Inheritance in Man #193300). In VHL disease, ELSTs often occur bilaterally and result in significant neurological disability, including deafness and disequilibrium.9,12 Despite the potentially devastating effects of ELSTs, the mechanisms of audiovestibular dysfunction, early imaging findings, and indications for surgical treatment have not been completely defined.

A disproportionately large fraction of patients with VHL disease present with clinical signs and symptoms of vestibuloocular dysfunction but no neuroimaging evidence of ELST.1,12 It has been hypothesized that the audiovestibular symptoms in at least some of these patients are the result of a “microscopic” ELST not detectable on routine imaging studies and that the mechanisms that underlie symptom formation may include tumor-related endolymphatic hydrops and/or intralabyrinthine hemorrhage.1,7,12 However, these hypotheses have not been confirmed by imaging studies or clinical experience. We describe a unique case involving a patient with VHL disease and audiovestibular dysfunction who was discovered at the time of surgery to have a small ELST and in whom neuroimaging revealed no abnormal finding other than intralabyrinthine hemorrhage.
Case Report

History and Presentation. This 33-year-old man with VHL disease presented in 1995 with sudden hearing loss, tinnitus, and vertigo. Audiometry revealed moderate-to-severe left-sided sensorineural hearing loss (Fig. 1A), but the results of an MR imaging study of the brain performed at that time were normal (Fig. 1B). Oral steroid therapy resulted in amelioration of vertigo, although the patient’s hearing loss was not affected by treatment. Four years later the patient presented with a recurrence of vertigo, tinnitus, and further deterioration in hearing (Fig. 1C). The T1- and T2-weighted MR images obtained at that time showed no lesion, but FLAIR sequences demonstrated hyperintensity within the left labyrinth consistent with hemorrhage (Fig. 1D and E). The patient was treated with oral steroids, and his tinnitus and vertigo improved.

Examination. In 2005, the patient presented again with complaints of progressive vertigo, tinnitus, and left-sided hearing loss. Audiometric evaluation revealed profound left-sided sensorineural hearing loss (Fig. 1F). Contrast-enhanced T1-weighted MR images of the temporal bones showed no evidence of tumor (Fig. 1G), and FLAIR sequences showed evidence of resolving hemorrhage (Fig. 1H).

Operation and Histopathological Findings. Based on the patient’s VHL disease status, progressive audiovestibular findings, and the results of previous inner ear imaging studies, we decided to perform surgical exploration of the endolymphatic sac and duct via a left retrolabyrinthine posterior petrosectomy. Intraoperatively a small (2-mm) ELST was identified within the endolymphatic duct within the osseous vestibular aqueduct. The endolymphatic duct was removed en bloc with the tumor and the endolymphatic sac was resected with the immediate surrounding posterior fossa dura. Histopathological examination of the tumor demonstrated a cystic papillary neoplasm composed of papillary epithelium lined by cuboidal cells with minimal nuclear pleomorphism, and it confirmed that the tumor was an ELST (Fig. 2). Postoperatively, the patient had improvement of his vertigo and tinnitus.

Discussion

Von Hippel–Lindau Disease and ELSTs

Von Hippel–Lindau disease is an autosomal-dominant neoplastic disorder associated with a germline mutation or deletion in the VHL gene located on the short arm of chromosome 3. Patients with VHL disease are predisposed to the development of both benign and malignant visceral and central nervous system lesions. Visceral lesions include renal cysts, renal cell carcinoma, pancreatic cysts, pancreatic neuroendocrine tumors, pheochromocytomas, and cystadenomas of the adnexal reproductive organs (broad ligament in females and epididymis in males). Central nervous system lesions include hemangioblastomas of the retina, cerebellum, brainstem, and spinal cord, as well as ELSTs.

Endolymphatic sac tumors were established as part of the VHL syndrome in 1997 by Manski and colleagues. While ELSTs rarely occur in individuals who do not have a mutation or deletion of the VHL gene, these lesions are found frequently in patients with VHL disease (occurring in 11 to 16%). Von Hippel–Lindau disease is the only condition associated with bilateral ELSTs, and approximately 30% of the patients with VHL disease who do have
Patients with VHL disease who have neuroimaging evidence of an ELST present with hearing loss (95–100%), tinnitus (92%), vertigo or dysequilibrium (62%), aural fullness (29%), and facial paresis (8%) that can be attributed to the lesion seen on the neuroimages. Hearing loss associated with imaging-evident ELSTs has been reported to occur suddenly and in a clinically significant degree (in 43% of cases) or in a stepwise progressive manner (also in 43% of cases) over 3 to 6 months. Occasionally, patients (14%) have reported a more gradual progressive hearing loss. Despite the correlation between ELSTs identified on neuroimages and symptoms, in a large proportion (60%) of the cases of VHL disease in which patients have vestibulocochlear symptoms, there is no imaging evidence of ELSTs. The underlying cause of these symptoms is unknown but there is evidence to suggest that in some patients the audiovestibular symptoms could be due to a “microscopic” ELST not obviously detectable on routine imaging studies. We describe a patient with VHL disease who had an ELST and in whom, despite significant audiovestibular findings, there was no neuroimaging evidence of an ELST except intralabyrinthine hemorrhage. Neuroimaging of ELSTs

Based on the association of ELSTs in VHL disease, serial high-resolution MR imaging and CT studies are now routinely used for the evaluation and follow-up of patients with this disorder. Nonenhanced T1-weighted MR imaging typically reveals ELSTs as heterogeneous or homogenous in signal intensity within or adjacent to the endolymphatic sac. On contrast-enhanced T1-weighted MR images, ELSTs can appear as homogenous or heterogeneously enhancing.

We began using FLAIR MR imaging sequences at our institution in 1999, which is when this patient’s hemorrhage was first detected. Fluid attenuated inversion recovery is particularly helpful in the evaluation of ELSTs following hemorrhage because these tumors contain an increased concentration of protein due to increased vascular permeability and inflammation secondary to cell disruption in the inner ear. The increased protein concentration is reflected by high signal intensity on FLAIR MR imaging. The FLAIR sequences were critical to the detection of the tumor in this case because there was no evidence of tumor or hemorrhage on standard enhanced and nonenhanced T1- and T2-weighted MR images.

We also routinely use high-resolution CT scanning of the temporal bones in conjunction with MR imaging for the diagnosis and evaluation of ELSTs. Computed tomography is a highly sensitive technique for demonstrating a destructive or expansive ELST centered in the region of the osseous vestibular aqueduct (between the internal auditory canal and sigmoid sinus).Mechanisms of Audiovestibular Dysfunction Associated With ELSTs

Disruption of the endolymph fluid homeostasis can result in pathological conditions associated with audiovestibular findings (for example, Ménière disease) similar to those described in patients with VHL disease with and without imaging evidence of ELSTs. The tumor within the endolymphatic sac along with inflammatory processes in the endolymphatic system, such as hemorrhage, can disrupt normal endolymph fluid homeostasis leading to endolymphatic hydrops and the development of audiovestibular symptoms, including hearing loss.

Authors of previous reports have suggested that hearing loss and other audiovestibular dysfunction associated with ELSTs may be the result of direct invasion of the otic capsule and membranous labyrinth of the semicircular canals or cochlea by tumor. Because many of these reports were published before specific high-resolution CT and MR imaging protocols were instituted (particularly in cases of VHL disease), previously described ELSTs were diagnosed after they had become large and had invaded the otic capsule. The underlying cause of hearing loss and vertigo in such cases is the destruction of the inner ear apparatus and endolymphatic flow within these anatomically interconnected structures.

Postmortem temporal bone histological findings in cases of VHL disease with ELSTs as well as recent improvements in imaging studies have led to the hypothesis that mechanisms other than the direct invasion of the labyrinth by tumor may underlie the audiovestibular dysfunction observed in patients with ELSTs, particularly the many patients with VHL disease who do not have neuroimaging evidence of ELSTs. Specifically, pathological processes including endolymphatic hydrops or inflammation from peritumoral hemorrhage into the labyrinth have been proposed to explain the vestibulocochlear signs and symptoms associated with ELSTs that have not invaded the otic capsule. Tumor-related endolymphatic hydrops could result from tumor-impaired endolymphatic resorption or excess peritumoral production of fluid. The excess production of peritumoral fluid into the membranous labyrinth, which can also result in hydrops, is analogous to the formation of peritumoral edema and cysts that are frequently associated with central nervous system hemangioblastomas and visceral tumors in VHL disease. The presence of endolymphatic hydrops in the setting of an ELST may explain the Ménière disease–like clinical syndrome (hearing loss, tinnitus, and
Vertigo) that affected our patient and other previously described patients with ELSTs.

Acute intralabyrinthine hemorrhage by the tumor could explain the frequent occurrence of irreversible, sudden, and significant hearing loss that occurs in patients with ELSTs.

This hypothesis is supported by the MR imaging evidence of intralabyrinthine hemorrhage coinciding with sudden hearing loss in our patient as well as a previously reported case in which acute hearing loss occurred in a patient who had intralabyrinthine hemorrhage and a tumor that was ob-

**FIG. 3.** Possible mechanisms of hearing loss associated with ELSTs. Normally endolymph circulates through the inner ear in a longitudinal manner toward the endolymphatic sac and duct where it is reabsorbed by the stria vascularis in the cochlea. Disruption of the production of endolymph, its circulation, or its reabsorption can result in pathological conditions associated with audiovestibular findings similar to those described in patients with VHL disease with and without evidence of ELSTs on neuroimaging. *Left:* Illustration of the normal right petrous temporal bone and associated anatomical structures, including the petrous internal carotid artery and the seventh and eighth cranial nerves. *Right:* Three potential mechanisms of hearing loss and audiovestibular dysfunction. *Upper:* Direct invasion by larger tumors through the otic capsule can result in hearing loss by destruction of the membranous labyrinth, semicircular canals, and/or cochlea. *Center:* An ELST-associated acute intralabyrinthine hemorrhage can disrupt longitudinal flow of endolymph and may lead to the development of audiovestibular symptoms, including hearing loss. *Lower:* Hydrops may result from blockage of the endolymphatic sac’s reabsorption of endolymph, inflammation in response to hemorrhage, and/or excessive production of fluid by an ELST, resulting in increased pressure within the membranous labyrinth (inset).
vious on neuroimages, and an autopsy case demonstrating hemosiderin in the utricular macular region of a deaf patient who had VHL disease and an ELST. The irreversibility of hearing loss in these patients may be the result of cochlear nerve degeneration secondary to inner ear injury by hemorrhage and/or secondary inflammation.

Indications for ELST Resection
Because small ELSTs can be successfully resected without surgery-associated hearing loss and because symptom formation is not linked to tumor size and is unpredictable, it may be reasonable to resect these neoplasms before they produce audiovestibular deficits. Thus we propose that patients with imaging evidence of ELSTs undergo surgery to prevent audiovestibular morbidity. Patients who have lost their hearing but have imaging evidence of an ELST should undergo resection if neurological compromise/compression or additional clinical signs/symptoms are present. Because intralabyrinthine hemorrhage may be an early indicator of a “microscopic” ELST in VHL disease, patients with VHL disease with hearing and lack of imaging evidence of ELST but evidence of intralabyrinthine hemorrhage (on recent or remote imaging) are also candidates for surgical intervention.

Conclusions
Endolymphatic sac tumors are a common cause of vestibulocochlear dysfunction in patients with VHL disease. Because resection is curative, patients with signs and symptoms of vestibulocochlear dysfunction may benefit from early surgery. An early sign of ELST in patients with VHL disease who suffer from otherwise unexplained audiovestibular dysfunction may be evidence of intralabyrinthine hemorrhage on MR images.

References