Neurologic Manifestations of von Hippel-Lindau Disease

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Neurologic Manifestations of von Hippel-Lindau Disease

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Russell R. Lonser, MD

CASE PRESENTATION

This 39-year-old woman was first evaluated at the National Institutes of Health (NIH) in August 2003. Three years before assessment, she experienced an acute episode of vertigo and left tinnitus. Magnetic resonance imaging (MRI) of the brain and temporal bones was unremarkable, and an audiogram revealed normal hearing. Her symptoms were attributed to Ménière disease and she was placed on a low-sodium diet without relief. Twenty-four months later, the patient experienced an episode of sudden left hearing loss coinciding with acute exacerbation of vertigo and left tinnitus. An audiogram confirmed a mild to severe left sensorineural hearing loss. Magnetic resonance imaging demonstrated hemorrhage in the left labyrinth but no evidence of endolymphatic sac tumor (ELST). The patient was continued on a low-sodium diet without relief of audovestibular signs or symptoms.

Nine months after the patient’s hearing loss, her mother was clinically diagnosed with von Hippel-Lindau disease (VHL) after she was found to have bilateral renal cell carcinomas (RCCs), pancreatic cysts, and central nervous system (CNS) hemangioblastomas. The clinical diagnosis was confirmed by VHL germline mutation testing. Subsequently, the patient was confirmed to have VHL by clinical criteria and VHL gene germline mutation testing. The patient was referred to the NIH, and in the week before evaluation, she experienced sudden onset of vertigo and left tinnitus with concomitant acute left hearing loss (confirmed by audiometry). Computed tomography (CT) and MRI again demonstrated left intralabyrinthine hemorrhage and a small ELST in the left vestibular aqueduct. Magnetic resonance imaging of the craniocaudal axis revealed hemangioblastomas of the medullary obex and thoracic spinal cord (FIGURE 1). Computed tomography of the abdomen revealed bilateral RCCs, renal cysts, and pancreatic cysts (FIGURE 2). Four weeks after evaluation, the ELST was resected, resulting in resolution of her vertigo and tinnitus. Her hearing loss remained unchanged. Bilateral partial nephrectomies were performed to resect mult

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multiple RCCs the month before and after ELST resection.

Eighteen months after ELST resection (19 months after initial NIH evaluation), the patient returned with new complaints of headaches, frequent hiccups, and swallowing difficulties. Craniospinal MRI at that time revealed development of a peritumoral cyst associated with the obex hemangioblastoma (Figure 1). To alleviate her symptoms, the patient underwent resection of the obex hemangioblastoma. Postoperative MRI revealed complete tumor removal and cyst resolution. The patient’s brainstem signs and symptoms resolved (follow-up time, 21 months). Serial abdominal CT revealed stable renal cysts, RCC, and pancreatic cysts. Details regarding the clinical features, diagnosis, and treatment related to this patient’s ELST have been published previously.1,2

**DISCUSSION**

**von Hippel-Lindau Disease**

von Hippel-Lindau disease is an autosomal-dominant neoplasia syndrome (prevalence of 1 in 39 000 live births)3 that is the result of a germline mutation of the VHL gene.4,5 Despite variable expression, VHL has greater than 90% penetrance by 65 years of age.6 Patients with VHL are predisposed to develop specific CNS and visceral lesions (TABLE 1).7,8 In the CNS, tumors can develop, including hemangioblastomas and ELSTs. In the viscera, renal cysts, RCCs, pancreatic cysts, pancreatic neuroendocrine tumors, pheochromocytomas, and cystadenomas of the reproductive adnexal organs can develop. Before the advent of routine surveillance and better-defined treatment recommendations for VHL-associated lesions (TABLE 2), median survival was 50 years of age,8,10 and the primary cause of death was from complications linked to CNS hemangioblastomas or RCCs.

**Diagnosis**

Diagnosis of VHL can be established by clinical criteria or genetic testing. Pa-
tients with a family history of VHL and a CNS hemangioblastoma, RCC, pheochromocytoma, or ELST meet the clinical criteria for diagnosis of VHL. Approximately 20% of patients do not have a family history but fulfill the clinical diagnostic criteria for VHL if they have 2 or more CNS hemangioblastomas or 1 CNS hemangioblastoma and a VHL-associated visceral tumor. Frequent, at-risk patients undergo testing for a germline VHL mutation. Detection rate of VHL mutations in patients with a family history of VHL is nearly 100%. However, de novo mutations in patients without a family history may result in a disease mosaicism where some but not all tissues carry the mutation. These patients may test negative if their peripheral blood leukocytes do not carry the VHL gene mutation.

Molecular Pathogenesis

The VHL tumor suppressor gene was mapped to the short arm of chromosome 3 by Seizinger and colleagues in 1988 and isolated by Latif and colleagues in 1993. Similar to our patient, most patients with VHL inherit a VHL gene (allele) with a germline mutation from the affected parent and a normal (wild-type) VHL gene from the unaffected parent. Although all cells have a VHL germline mutation in patients who inherit the trait, tumors only form in cells that have lost function of the wild-type allele and that are located within specific VHL-susceptible target organs.

The VHL gene is widely expressed in tissues, including those not affected by VHL. VHL messenger RNA encodes for VHL protein (pVHL). Posttranslation, pVHL complexes with elongin B, elongin C, Rbx1, and cullin 2, forming an ubiquitin ligase that proteolyzes the α subunit of hypoxia-inducible factor (HIF). Under normal circumstances, HIF coordinates cellular response to hypoxia through transcriptional regulation. Hypoxia-inducible factor enhances cellular metabolism and increases the expression of angiogenic and mitogenic factors. Some of these factors include vascular endothelial growth factor (VEGF), platelet-derived growth factor β chain (PDGF-β), erythropoietin, and transforming growth factor (TGF). With absent or abnormal pVHL function, HIF may constitutively stimulate angiogenesis via increased levels of VEGF or PDGF-β, explaining the vascular nature of VHL-associated tumors. VEGF-mediated increased tumor vascular permeability may be the cause of the frequent formation of peritumoral edema and cysts in VHL. HIF-mediated development of autocrine loops by the overproduction of TGF-α or erythropoietin in conjunction with overexpression of their respective receptors may also underlie tumorigenesis.

Tumorigenesis, independent of HIF regulation, may be caused or enhanced solely by absent or abnor-

### Table 1. Approximate Distribution, Age of Onset, and Frequency of Lesions Associated With von Hippel-Lindau Disease (Adapted From Lonser et al)

<table>
<thead>
<tr>
<th>Location</th>
<th>Age of Onset, Mean (Range), y</th>
<th>Frequency of Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinal hemangioblastomas</td>
<td>25 (1-67)</td>
<td>25-60</td>
</tr>
<tr>
<td>Craniospinal hemangioblastomas</td>
<td>33 (9-78)</td>
<td>60-80</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>33 (9-78)</td>
<td>44-72</td>
</tr>
<tr>
<td>Brainstem</td>
<td>32 (12-46)</td>
<td>10-25</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>32 (12-66)</td>
<td>13-50</td>
</tr>
<tr>
<td>Supratentorial</td>
<td>34 (Unknown)</td>
<td>3-6</td>
</tr>
<tr>
<td>Lumbosacral nerve roots</td>
<td>Unknown</td>
<td>1-3</td>
</tr>
<tr>
<td>Endolymphatic sac tumors</td>
<td>22 (12-50)</td>
<td>10-15</td>
</tr>
<tr>
<td>Visceral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal cell carcinoma/cysts</td>
<td>39 (16-67)</td>
<td>25-60</td>
</tr>
<tr>
<td>Pheochromocytomas</td>
<td>30 (5-58)</td>
<td>10-20</td>
</tr>
<tr>
<td>Pancreatic neuroendocrine tumor</td>
<td>38 (16-68)</td>
<td>8-17</td>
</tr>
<tr>
<td>Pancreatic cyst</td>
<td>36 (5-70)</td>
<td>17-56</td>
</tr>
<tr>
<td>Epididymal cystadenoma</td>
<td>Unknown</td>
<td>25-60</td>
</tr>
<tr>
<td>Broad ligament cystadenoma</td>
<td>Unknown (16-46)</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
mal pVHL. Cells lacking pVHL lose the ability to exit the cell cycle, which could be an early event in VHL tumorigenesis. Absence of pVHL may further increase VEGF expression through the release of transcriptional and posttranslational regulation. Cells lacking pVHL cannot properly assemble a fibronectin extracellular matrix.

### VHL-Associated Lesions (Excluding Craniospinal Hemangioblastomas and ELSTs)

**RCC and Renal Cysts.** Renal cell carcinoma is the most common malignant neoplasm in VHL (Table 1). An RCC or cyst can be found in 60% of patients. Renal cysts are typically asymptomatic and seldom need treatment. However, complex cysts need serial monitoring because they often harbor solid components of RCC. Although small RCCs tend to be low-grade and minimally invasive, the growth rate of these lesions is highly variable. Because RCCs can remain asymptomatic for long periods of time, serial imaging is useful for early diagnosis (Table 2). Rarely, in more advanced cases, patients present with hematuria, flank pain, or a flank mass. Some clinicians recommend nephron-sparing resection of RCCs when the largest tumor reaches a maximum diameter of 3 cm. Nephron- or renal-sparing surgery is based on the ability to preserve renal function while reducing the risk of metastasis. Walther and colleagues reported that renal-sparing surgery for RCCs smaller than 3 cm was not associated with metastasis or need for renal transplantation or dialysis. Tumor enucleation or partial nephrectomy may be needed for resection of tumors larger than 3 cm. Less invasive percutaneous treatments of RCC are being explored.

**Pancreatic Neuroendocrine Tumors and Cysts.** Thirty-five percent to 70% of patients with VHL develop a pancreatic neuroendocrine tumor or cyst (Table 1). Pancreatic cysts are generally asymptomatic and do not require treatment. Pancreatic neuroendocrine tumors are often nonfunctional and asymptomatic but can behave malignantly in up to 8% of cases. These tumors are identified on postcontrast abdominal CT or MRI (Table 2). Recent data indicate that optimal timing of surgical resection of pancreatic neuroendocrine tumors may be based on tumor size, exon 3 VHL mutation status, and tumor doubling time.

**Pheochromocytoma.** Pheochromocytomas can be multiple and bilateral in nature in VHL (Table 1). They can also be found as extra-adrenal paragangliomas in the carotid body, glomus jugulare, and periaortic tissues. Five percent of pheochromocytomas are malignant. Frequent clinical findings associated with pheochromocytomas include intermittent or sustained hypertension, palpitations, tachycardia, headaches, episodic sweating, pallor, and nausea, but 30% of patients with pheochromocytomas are asymptomatic. The diagnosis of pheochromocytoma is made by laboratory and imaging studies (Table 2). Preoperative evaluation is critical in patients with VHL to prevent a perioperative hypertensive crisis. Early intervention with adrenal cortical-sparing surgery results in low recurrence and long-term corticosteroid independence.

**Cystadenomas of Reproductive Adnexal Organs.** Cystadenomas of the epididymis and broad ligament are benign lesions that can be found frequently in patients with VHL (Table 1). They are often bilateral and multiple. They can be identified by ultrasound (epididymal) or abdominal CT (broad ligament). Because these lesions are benign and most often symptom-free, they are managed conservatively.

**Retinal Hemangioblastomas.** Retinal hemangioblastomas are often bilateral and multifocal in VHL (Table 1). They can arise in the periphery and near or on the optic disk. Despite frequently being asymptomatic, they can cause visual symptoms by progressive growth, edema, or development of hard exudates. Ophthalmoscopy with iridodialysis allows identification of most retinal hemangioblastomas. Early diagnosis and treatment (photocoagulation and cryotherapy) of peripheral tumors can prevent visual loss.

**Craniospinal Hemangioblastomas**

**Epidemiology.** Craniospinal hemangioblastomas are the most common tumor associated with VHL (Table 1). Sixty to 80% of patients with VHL develop a CNS hemangioblastoma of the cerebellum, brainstem, or spinal cord. Nearly all of these patients (90%) develop multiple hemangioblastomas. Despite their benign histology, hemangioblastomas can cause significant morbidity and mortality in VHL.

### Table 2. Suggested Surveillance Modalities and Frequency for Neurologic Manifestations of von Hippel-Lindau Disease (Adapted From Choyke et al)

<table>
<thead>
<tr>
<th>Lesions Evaluated</th>
<th>Start Age (Frequency)</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinal hemangioblastoma</td>
<td>Infancy (yearly)</td>
<td>Ophthalmoscopy</td>
</tr>
<tr>
<td>Craniospinal hemangioblastoma</td>
<td>Age 11 y (yearly)</td>
<td>MRI of craniospinal axis</td>
</tr>
<tr>
<td>Endolymphatic sac tumor</td>
<td>Onset of symptoms, such as hearing loss, tinnitus, vertigo, or unexplained balance difficulties</td>
<td>CT and MRI of internal auditory canals</td>
</tr>
<tr>
<td>Endolymphatic sac tumor</td>
<td>When clinically indicated</td>
<td>Audiologic function tests</td>
</tr>
<tr>
<td>Renal carcinoma/cyst, pancreatic neuroendocrine tumor/cyst</td>
<td>Age 8 y (yearly; MRI as clinically indicated)</td>
<td>Ultrasound of abdomen</td>
</tr>
<tr>
<td>Renal carcinoma/cyst, pancreatic neuroendocrine tumor/cyst</td>
<td>Age 18 y or earlier if clinically indicated (yearly)</td>
<td>CT of abdomen</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Age 2 y (yearly and when blood pressure is elevated)</td>
<td>Plasma or 24-h urinary catecholamines and metanephrines</td>
</tr>
</tbody>
</table>

**Abbreviations:** CT, computed tomography; MRI, magnetic resonance imaging.

*Imaging typically performed with and without intravenous contrast.*

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nervous system hemangioblastomas (outside the retina) are found nearly exclusively (95% of tumors) in the brainstem, cerebellum, or spinal cord. 7,20,30

**Imaging Findings.** Contrast-enhanced MRI is the most sensitive and accurate imaging modality for detecting and monitoring hemangioblastomas. Hemangioblastomas vividly and discretely enhance on T1-weighted MRI sequences. Even small tumors (2 mm in diameter) are reliably detected and precisely characterized over serial studies. Using MRI is critical to detect the development or changes in peritumoral edema and cysts using fluid-attenuated inversion recovery and T2-weighted sequences.

**Presenting Signs and Symptoms.** Signs and symptoms related to CNS hemangioblastomas are attributable to the anatomic region where they arise. Cer-ebellar hemangioblastomas cause headache (75% of patients), gait ataxia (55%), dysmetria (29%), hyposthesia (28%), and nausea or vomiting (28%). 31 Brainstem hemangioblastomas cause hypesthesia (55%), gait ataxia (22%), dysphagia (22%), hyper-reflexia (22%), and headache (11%). 7,32 Spinal cord hemangioblastomas cause hyposthesia (83%), weakness (65%), gait ataxia (65%), hyperreflexia (52%), and pain (17%). 7

**Natural History.** To better define the natural history of VHL-associated hemangioblastomas, Wanebo and colleagues 30 reviewed the imaging and clinical features of 160 consecutive patients with VHL harboring 655 CNS hemangioblastomas followed up at the NIH (mean [SD] follow-up time, 21 [27] months). The clinical circumstance was dynamic and tumors were found to have variable growth patterns. Although symptom formation appeared to be associated with tumor size, tumor growth rate, and the presence of a peritumoral cyst, no reliable threshold for tumor size or growth could be identified that would predict symptom formation and need for treatment.

Ammerman and colleagues 25 studied the pattern of growth of CNS hemangioblastomas in 19 patients with VHL who had serial images taken for at least 10 years. Hemangioblastomas grew in a saltatory growth pattern consisting of periods of rapid growth followed by periods of quiescence (97% of 143 tumors). Hemangioblastomas had an average of 1.85 quiescent periods between growth periods before becoming symptomatic and requiring resection. Periods of growth lasted an average (SD) of 13 (15) months while the periods of quiescence averaged 25 (19) months. Nearly all of the hemangioblastomas (97%) demonstrated radiographic progression, but only 50% required treatment for symptom formation. Nearly half of tumors (45%) that required resection (symptomatic) were not apparent on initial MRI.

**Peritumoral Cyst Formation.** Although the development of signs and symptoms can occasionally be directly attributed to the mass effect of the hemangioblastoma, neurologic dysfunction is caused most frequently by the combined mass effect of tumor and an associated peritumoral cyst (Figure 1). Most symptomatic cerebellar and brainstem hemangioblastomas (70%) are associated with a peritumoral cyst, and more than 90% of symptomatic spinal hemangioblastomas are associated with a peritumoral cyst (syringomyelia). 32,33 In such cases, the cyst accounts for the bulk of the mass burden. Specifically, the average cyst volume in the cerebellum was 4 times larger than the associated tumor, and in the brainstem it was 12 times larger than the associated tumor in symptomatic patients. Conversely, a small fraction of asymptomatic cerebellar, brainstem, or spinal cord hemangioblastomas (5%-10%) are associated with peritumoral cysts.

Understanding the mechanism underlying peritumoral cyst development and propagation with VHL-associated hemangioblastomas has led to several critical clinical insights (FIGURE 3). 34,35 Because the tumor is the source of peritumoral edema/cyst formation, edema/cyst resolution after tumor removal occurs reliably and treatment does not require cyst wall resection or fenestration. Reducing tumor vascular permeability could be beneficial, and clinical improvements using anti-VEGF therapies have been associated with edema reduction despite having no effect on tumor size. 36,37 Increasing vascular permeability can be deleterious, and studies have shown that radiation induces transient increases in vascular permeability that can lead to peritumoral edema and cyst formation, suggesting judicious irradiation of hemangioblastomas with significant peritumoral edema/cysts. 38 Finally, peritumoral cysts can stop growing when the surface area of the cyst wall is sufficiently large to absorb the excess fluid and become quiescent and remain asymptomatic. Imaging evidence of edema and cyst formation in asymptomatic patients with VHL is not an absolute indication for surgery.

**Tumor Features.** Grossly, hemangioblastomas appear bright red or orange/yellow in color and are invariably associated with intense vascularity (Figure 3). Histologically, hemangioblastomas have characteristic features that include proliferation of stromal cells and endothelial cells (World Health Organization grade 1) (Figure 3). 39 Endothelial cells form vascular channels around the neoplastic stromal cells. 40 Stromal cells have numerous lipid-containing vacuoles that result in the clear cell morphology similar to RCC. Because patients with VHL often have contemporaneous RCCs that can metastasize to CNS tissues or hemangio- blastomas, 39,41 immunohistochemical differentiation between RCC and hemangioblastoma may be necessary.

**Developmental Origin.** Based on embryologic findings and evidence of intratumoral hematopoiesis and endothelial cell formation, it was hypothesized that hemangioblastomas may derive from an embryologic cell capable of blood and vessel formation. This theory was not directly testable until 1998, when Choi and
Craniospinal hemangioblastomas are highly vascular benign tumors that arise frequently in patients with von Hippel-Lindau disease.

The capillary proliferation and increased vascular permeability of these tumors are thought to be mediated, at least in part, by dysregulation of the hypoxia-inducible factor pathway and excess expression of vascular endothelial growth factor (VEGF) by tumor stromal cells.

Interventions that reduce vascular permeability (eg, anti-VEGF therapy) can reduce fluid extravasation from the hemangioblastoma. This can lead to decreased peritumoral edema or reduction in peritumoral cyst size leading to improvements in associated clinical symptoms without decreasing tumor volume.36,37

Because the hemangioblastoma is the source of peritumoral edema and cyst formation, resection of the tumor itself will result in resolution of edema and collapse of the cyst.31,34

Serial axial enhanced magnetic resonance images demonstrate peritumoral cyst collapse in a patient after removal of a hemangioblastoma (arrowhead) and re-expansion of the surrounding cerebellar folia.
colleagues characterized a common embryologic precursor cell that was transiently present during mesoderm development and was capable of blood and endothelial cell formation. They defined this multipotent embryologic cell as a hemangioblast. Subsequent investigations uniquely identified the embryonic hemangioblast by coexpression of brachyury, Flk1 (VEGF receptor 2), and Scl (stem cell leukemia). Similar to the embryonic hemangioblast, the neoplastic stromal cells in hemangioblastomas coexpressed brachyury, Flk1, and Scl.

**Treatment.** Complete resection of hemangioblastomas is curative and most craniospinal hemangioblastomas can be resected safely. Because of the multiplicity of CNS hemangioblastomas, and because their growth rate is unpredictable, surgery is generally reserved until associated symptoms arise. Using this strategy, most patients with VHL can maintain excellent neurologic function and unnecessary surgical resection can be avoided.

Stereotactic radiosurgery has been investigated as a potential therapeutic option. Small hemangioblastomas not associated with peritumoral cysts may respond best to radiotherapy. Although some studies have established the successful use of radiosurgery based on stability of tumor size, lack of hemangioblastoma progression in these cases may represent a quiescent period and not a response to treatment. Longer-term assessment of more patients is necessary to determine the effectiveness of this treatment and the potential risk of developing new neoplasms in patients with a constitutional haploinsufficiency.

**Endolymphatic Sac Tumors**

**Epidemiology.** Endolymphatic sac tumors were first established as a distinct pathologic entity by Heffner in 1989 and were recognized as part of VHL syndrome by Manski and colleagues in 1997. Imaging evidence of an ELST can be found in approximately 10% to 15% of patients with VHL, and 30% of VHL patients with an ELST develop bilateral ELSTs. Despite their benign histology, ELSTs are locally invasive tumors that cause audiovestibular morbidity, including hearing loss, vertigo, tinnitus, and auricular pain.

**Imaging Findings.** Optimal identification of ELSTs requires high-resolution CT and MRI. On CT images, ELSTs are soft tissue density tumors that expand, destroy, and incorporate the adjacent temporal bone. Small bony erosions adjacent to the vestibular aqueduct may be evident on CT as an initial radiographic finding of an ELST. On MRIs, ELSTs can have considerable heterogeneity because internal hemorrhage and cysts, incorporated temporal bone, cholesterol granuloma, and vascular flow voids may be present to varying degrees. Intra-labyrinthine hemorrhage, a common imaging feature associated with ELSTs, appears as a T1-weighted hyperintensity within the vestibule, cochlea, or semicircular canals distinct from the site of tumor.

**Presenting Signs and Symptoms.** Patients with VHL with imaging evidence of an ELST present with hearing loss (95% of patients), tinnitus (90%), vertigo or disequilibrium (66%), aural fullness (30%), and facial paresis (8%). Hearing loss can occur either acutely (86%) or gradually over several years (14%). Generally, once hearing loss occurs it is irreversible, and it typically occurs early in life (Table 1). Similar to our case, patients usually report that hearing loss coincides with the exacerbation of vestibular symptoms. A significant fraction of VHL patients with vestibulocochlear symptoms (59%) have no imaging evidence of ELSTs. The etiology of these clinical manifestations may be due to a microscopic ELST or hyperplasia of the endolymphatic epithelium in patients with VHL.

**Mechanisms of Hearing Loss.** To define ELST-associated mechanisms underlying audiovestibular pathophysiology, a prospective study of VHL patients with ELSTs was performed. Clinical and audiologic data were correlated with serial CT and MRI to elucidate the mechanisms underlying audiovestibular dysfunction. Although tumor invasion of the otic capsule (bony covering of the inner ear apparatus) (18% of patients) was associated with large ELSTs and caused hearing loss (100% of patients with otic capsule invasion), the majority of patients (82%) had small ELSTs that did not invade the otic capsule. In this group of patients, hearing loss was still present (91% of affected ears) and either developed suddenly (43%) or gradually (48%). Sudden hearing loss in these patients correlated with MRI evidence of intralabyrinthine hemorrhage, but hemorrhage was not seen in patients with gradual or normal hearing. Tumor size was not associated with the development of audiovestibular symptoms.

Findings from this study support 3 distinct mechanisms of ELST-associated audiovestibular morbidity, including direct invasion of the otic capsule by tumor, intralabyrinthine hemorrhage, and endolymphatic hydrops. First, direct ELST erosion into the inner ear can result in membranous labyrinth destruction that disrupts endolymphatic flow, causing hearing loss and vestibulopathy. Second, acute intralabyrinthine hemorrhage, as seen in patients with sudden hearing loss without otic capsule invasion, indicates that ELST-associated spontaneous hemorrhage conducted into the labyrinth via the endolymphatic duct may underlie the sudden hearing loss in these cases. This mechanism is further supported by the presence of hemosiderin in the membranous labyrinth of a deaf VHL patient with an ELST at autopsy. Finally, in patients with gradual hearing loss, no hemorrhage was identified and the symptom complex was similar to our patient and mimicked that of Ménière disease. Development of endolymphatic hydrops is another potential consequence of a small ELST. Hydrops represents an increase...
in endolymph volume, the regulation of which is thought to be the primary function of the endolymphatic sac. Because endolymph is primarily produced within the cochlea, hydrops in patients with ELSTs could develop via impaired endolymph resorption or due to excess production of fluid into the membranous labyrinth. Excess production of fluid by the ELST could be analogous to the formation of peritumoral edema or cysts associated with CNS hemangioblastomas and visceral tumors in VHL.3,7

Tumor Features. Grossly, ELSTs can appear bright or dark red in color. Histologically, ELSTs are well-vascularized papillary cystic glandular neoplasms lined by a row of cuboidal cells. Prominent pleomorphism is not seen and mitotic activity is absent.7 The ultrastructural features of these tumors are consistent with endolymphatic sac epithelium.47 Despite the lack of malignant features associated with ELSTs, they have been referred to as low-grade adenocarcinomas (rather than adenomas) of endolymphatic sac origin.57 Recent evidence indicates that ELSTs originate in the vestibular aqueduct portion of the endolymphatic sac and duct system.52

Developmental Origin. Studies have revealed multifocal, VHL-deficient epithelial cell proliferations throughout the endolymphatic duct and sac in patients with VHL. These proliferations may represent potential precursor structures for the development of frank tumor.50 The abundance of precursor structures detected in the endolymphatic sac and duct in a VHL patient without ELST at autopsy suggests that most precursor structures do not develop into tumors during a patient's lifetime.51

Treatment. Because audiovestibular morbidity is frequently associated with very small tumors and because irreversible hearing loss can occur suddenly independent of tumor size, early surgical intervention may be warranted. Complete resection of ELSTs is curative, can alleviate vestibular symptomatology, and can be performed with hearing preservation and minimal morbidity.23,43 To intervene early in patients with VHL, prompt diagnosis based on clinical findings and supported by high-resolution CT and MRI to detect small ELSTs and intralabyrinthine hemorrhage is warranted. Detection of an ELST may, after weighing potential risks, prompt surgery to ameliorate symptoms and prevent progression of hearing loss.

CONCLUSIONS

Recent investigations into VHL-associated CNS lesions have given insight into the origin and development of these tumors. Emerging data from imaging and clinical surveillance protocols have provided insights into the natural history of VHL-associated ELSTs and hemangioblastomas. Because of their differing natural histories, the optimal management strategies for the 2 neurologic manifestations of VHL are different.

Author Contributions: Dr Lonser had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Butman, Lonser. Acquisition of data: Butman, Linehan, Lonser. Analysis and interpretation of data: Butman, Linehan, Lonser. Drafting of the manuscript: Butman, Lonser. Critical revision of the manuscript for important intellectual content: Butman, Linehan, Lonser. Obtained funding: Butman, Linehan, Lonser. Administrative, technical, or material support: Butman, Linehan, Lonser. Study supervision: Butman, Lonser.

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REFERENCES