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Review Article

Nervous System Manifestations of von Hippel-Lindau Disease

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Abstract

von Hippel-Lindau (VHL) disease is a highly penetrant multiple organ heritable cancer syndrome with a spectrum of benign and malignant tumors. VHL is results from a germline mutation of the *VHL tumor suppressor gene* (short arm of chromosome 3). VHL affects 1 in 36,000 to 39,000 livebirths as an autosomal dominant trait. Individuals harboring a mutation in *VHL* can develop benign and malignant tumors, both of the central nervous system (CNS) and systemically. VHL-associated lesions of the CNS include retinal and craniospinal hemangioblastomas, as well as endolymphatic sac tumors (ELSTs). While CNS hemangioblastomas (most common tumor in VHL) and ELSTs are benign tumors, they are associated with significant neurologic morbidity and mortality based on their location and multiplicity. Because of the management complexities of this disease, multidisciplinary screening and treatment, as well as a deep understanding of the natural course of the disease are needed.

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INTRODUCTION

von Hippel–Lindau disease (VHL) (OMIM 193300) is an autosomal dominant heritable neoplastic syndrome typified by the frequent development of benign and malignant, vascular tumors in highly conserved topographic distribution [1]. Affected individuals can develop central nervous system (CNS) lesions including retinal and craniospinal hemangioblastomas, as well as endolymphatic sac tumors (ELSTs) of the temporal bone. Visceral VHL-associated lesions frequently include renal cell carcinomas, renal cysts, pheochromocytomas, extra-adrenal paragangliomas, pancreatic microcystic adenomas, pancreatic cysts, pancreatic neuroendocrine tumors, as well as cystadenomas of the epididymis and broad ligament (Figure 1) [2-12].

The disease eponym is derived from the German ophthalmologist, Eugen von Hippel, who described the retinal angioma ("angiomatosis retinae", which are currently referred to as retinal hemangioblastomas) [13] and the Swedish pathologist, Arvid Lindau, who associated hemangioblastomas of the retina and cerebellum with other VHL-associated visceral lesions [14]. VHL has an estimated incidence of 1 in 36,000 to 39,000 live births [15,16] and a penetrance of 90% by 65 years of age [17]. VHL is caused by an underlying germline mutation of *VHL* tumor suppressor gene. Tumor development occurs after inactivation of the wild-type allele [2,18-20]. Judicious multidisciplinary treatment of VHL-associated lesions has increased median life expectancy to 52.5 years [21].

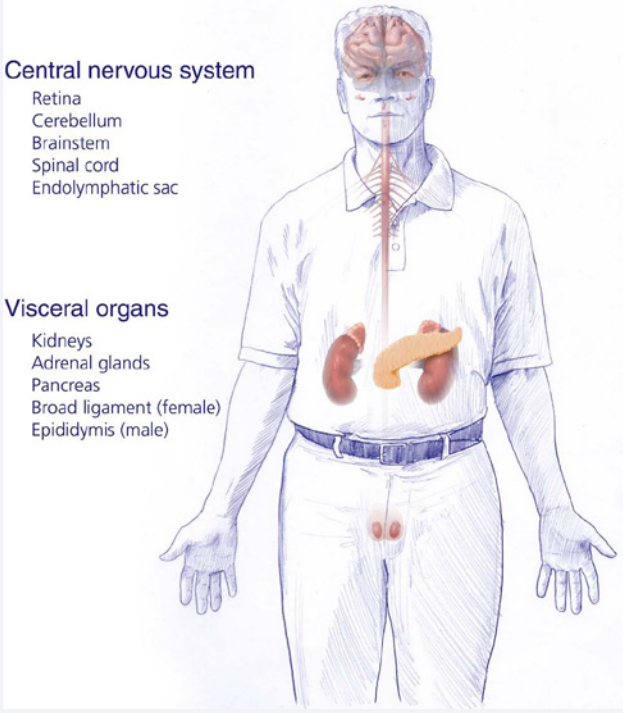

Figure 1 Affected organs in von Hippel Lindau Disease.

MOLECULAR GENETICS

The *VHL* gene is on the short arm of chromosome 3 (3p25–26) [22]. Germline mutations of *VHL* account for more than 95% of the patients affected by VHL [23,24]. Individuals inherit a *VHL* germline mutation from the carrier parent and a normal (wild type) gene from the non-affected parent [25]. Tumorigenesis occurs when the wild type *VHL* allele is inactivated (loss of heterozygosity) in defined susceptible target organs (Figure 1). Fifty percent of patients have somatic inactivation of the *VHL* gene in sporadically occurring hemangioblastomas [26-28] and renal cell carcinomas [29-32].

VHL is composed of 3 exons that encode for the 213 amino-acid protein (pVHL), which as a molecular weight of 30 kDa [22]. pVHL subcellular shuttling between the cytoplasm and nucleus may be due to posttranslational modification necessary for its oxygen sensing properties [33]. pVHL contains 2 functional domains, α and β. The α domain binds to elongin C recruiting elongin B and Cullin 2 (CUL2) to form the VCB-Cul2, an E3 ubiquitin-ligase complex, that targets substrates for proteasomal degradation (Figure 2) [34-37]. The substrate-recognition site for targeting proteins β domain [34-37].

VHL is critical for proteasomal degradation of hypoxia inducible transcription factor (HIF). HIF is basic helix-loop helix transcription factor that transcriptionally activates genes that participate in homeostatic responses to oxygen changes and, thereby, controls angiogenesis/vascularization, cell proliferation, apoptosis, cell differentiation and glucose metabolism. HIF1 is a heterodimer protein consisting of HIF1α and HIF1β. Under states of normoxia HIF1α is hydroxylated by prolyl hydroxylase 2 (PHD2), facilitating the binding of VCB-CUL2 complex tagging HIFα for ubiquitation and targeted degradation.

Under hypoxic conditions, the HIF1α-subunit is stabilized, accumulates and dimerizes with HIF1β. The dimer translocates to the nucleus and co-activates transcription of genes that contain hypoxia responsive elements (HREs). Currently, over than 200 genes have been identified to be target genes of HIF that contain the HRE sequence, including platelet derivative

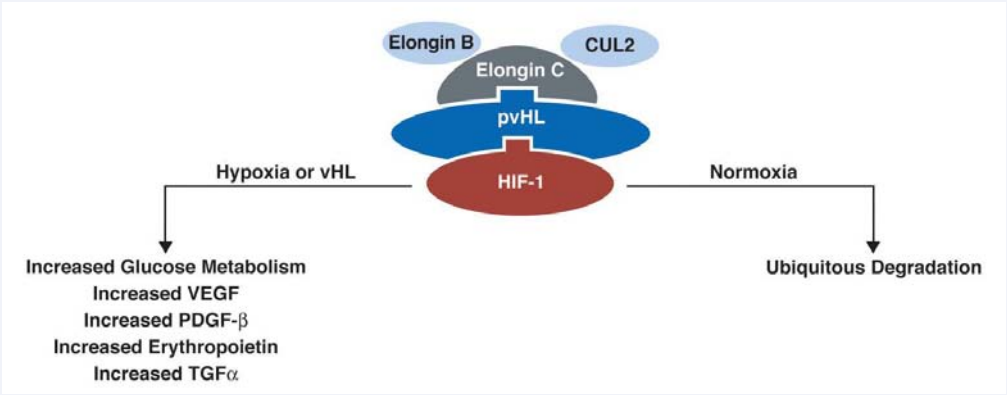

Figure 2 The VCB-CUL2 complex and the functions of the complex under normoxia and hypoxia. (Adapted from Lonser et. al., *Lancet* 2003) [1].

Table 1: VHL subtypes based on family linkage analysis and genotype-phenotype classifications.

	Clinical characteristics
Type 1	Retinal hemangioblastomas, CNS hemangioblastomas, Renal cell carcinoma, Pancreatic neoplasms and cysts
Type 2A	Pheochromocytomas, Retinal hemangioblastomas, CNS hemangioblastomas
Type 2B	Pheochromocytomas, Retinal hemangioblastomas, CNS hemangioblastomas, Renal cell carcinomas, Pancreatic neoplasms and cysts
Type 2C	Pheochromocytoma only

growth factor β (PDGFβ), transforming growth factor α (TGFα), vascular endothelial growth factor (VEGF), erythropoietin (EPO) and glucose transporter-1 (Glut-1) [38-41]. If VHL protein is absent or abnormal, HIF initiates transcription of genes favoring tumor development including those listed above, as well as those involved in extracellular matrix formation, vasculogenesis, chemotaxis, pH regulation and cell cycle regulation [20,42].

DIAGNOSIS

VHL can be diagnosed based on clinical criteria and/or genetic testing. In individuals with a family history of VHL, a craniospinal hemangioblastoma, retinal hemangiobastoma, renal clear cell carcinoma or pheochromocytoma are diagnostic. In individuals with no VHL family history, the diagnosis of VHL is made if they have 2 or more CNS hemangioblastomas, or 1 CNS hemangioblastoma and a visceral tumor (with the exception of renal and epididymal cysts) [5,43]. Genetic (germline) testing in VHL families using Southern blotting and DNA-sequence analysis is 100% [44]. However, in a study of 181 VHL kindreds, it was determined that postzygotic mosaicism was the mechanism in 2 (4.8%) of 42 parents. Consequently, mosaicism can be an infrequent cause for failure of a VHL molecular diagnosis [45].

Specific correlations have emerged between genotype and phenotype by linkage analysis, which has aided in providing screening and counseling of affected family members, and those with similar genetic aberrations (Table 1) [19,20,46-50].

CRANIOSPINAL HEMANGIOBLASTOMAS

General

Hemangioblastomas are highly vascular CNS tumors. They are a defining feature in VHL. They affect 80% or more of VHL patients and it is the most common tumor (CNS or visceral) associated with VHL [1,17, 43,51]. Mean age at symptom formation due to VHL-associated CNS hemangioblastomas is approximately 30 years and hemangioblastoma(s) are the presenting feature in half of VHL patients [7,52,53]. Although these tumors are benign, they are a leading cause of VHL-associated mortality and neurologic morbidity.

Natural history

Large scale VHL patient studies have shown that hemangioblastomas have a sporadic growth pattern with periods of growth followed by growth arrest ("saltatory growth pattern") [1,6-8,54]. Patterns of growth vary and are categorized as saltatory (72% of growing tumors), linear (6%), or exponential (22%). Many tumors will remain the same size for several years [7]. In recent studies [54], VHL patients were found to have a mean of 8.5 tumors/patient (range, 1 to 33 tumors/patients) at initial evaluation. Mean tumor development was 0.4 new tumors/year and was correlated with age (more frequent development in younger patients).

Hemangioblastomas are associated with edema and peritumoral cysts (approximately 10% of all CNS hemangioblastomas). Depending on location, the peritumoral cyst mass effect often has a greater capacity to cause signs/symptoms than the tumor itself (because of more rapid growth of the cyst compared to the tumor itself). Edema formation is the result of increased hemangioblastoma vascular permeability associated, in turn with increased interstitial pressure in the tumor. This results in plasma distribution by bulk flow into the adjacent tissue [55]. Once the capacity of the surrounding tissue to absorb the interstitial fluid is exceeded, cyst formation occurs. The walls of peritumoral cysts (when associated with hemangioblastomas) are lined by chronic astrocytosis with abundant Rosenthal fibers.

Table 2: Symptoms based on anatomic location of tumors.*

Location	Frequency	Percentage
Brainstem		
Headache	10	83.3%
Singultus	8	66.6%
Nausea/vomiting	6	50.0%
Dysphagia	5	41.7%
Cough	3	25.0%
Paresthesia	3	25.0%
Cauda equina		
Urinary/bowel abnormalities	5	100.0%
Pain	5	100.0%
Paresthesia	4	80.0%
Headache	2	40.0%
Cerebellum		
Headache	77	77.0%
Gait ataxia	57	57.0%
Nausea/vomiting	19	19.0%
Vertigo	18	18.0%
Speech difficulties	15	15.0%
Dysmetria	11	11.0%
Nerve root		
Cruciate paralysis	1	100.0%
Spine		
Paresthesia	28	75.7%
Pain	24	64.9%
Gait ataxia	13	35.1%
Dysesthesias	9	24.3%
Urinary/bowel abnormalities	7	18.9%
Supratentorial		
Vision disturbance/loss	2	50.0%
Weakness	2	50.0%

*, The symptoms listed here are the major symptoms recorded from patients that underwent resection of symptomatic tumors.

Clinical features

Signs and symptoms vary based on the location of the hemangioblastoma, edema and/or cyst (tumor volume, edema and/or cyst size) (Table 2). On average, tumors that become symptomatic and require resection grow faster than tumors that

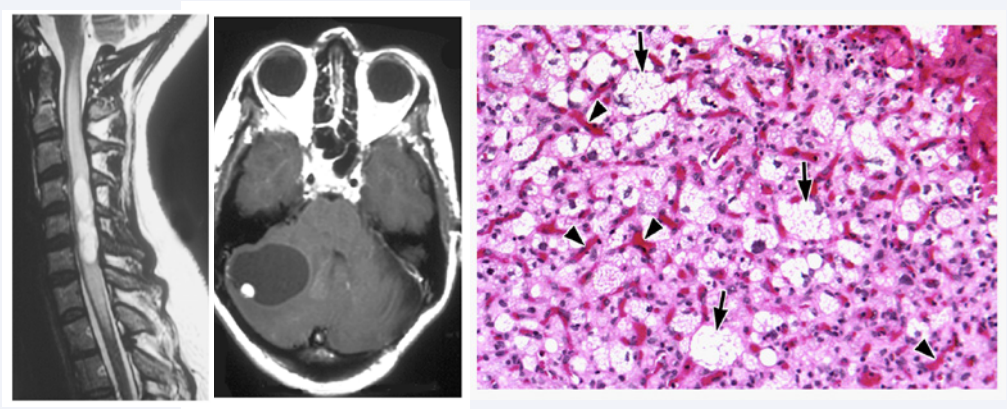

Figure 3 Diagnostic radiologic and histologic images of von Hippel-Lindau disease (VHL)-associated hemangioblastomas of the craniospinal axis. (Left panel) Sagittal T2-weighted magnetic resonance (MR)-imaging of an intramedullary homogenously enhancing hemangioblastoma with associated spinal cord edema. (Middle panel) Axial T1-weighted MR-image of a right cerebellar hemisphere hemangioblastoma associated with a peritumoral cyst. (Right panel) Hematoxylin and eosin staining demonstrating classic vascular elements (arrowheads) along with stromal vacuolated cells (arrows). Original magnification X 20. (Adapted from Lonser et. al. Ann Neurol, 2005) [55].

are asymptomatic. Similarly, associated peritumoral cysts that become symptomatic and require resection grow much faster (3.2-fold faster versus asymptomatic lesions at 1.7-fold) than the tumors they are associated with [7].

Radiologic findings

Hemangioblastomas are best visualized by contrast-enhanced T1-weighted MR-imaging. T2-weighted MR-imaging allows excellent quantification of edema and peritumoral cysts. Arteriography can be used to highlight the arteriovenous shunting and early draining veins associated with these tumors prior to resection (Figure 3).

Origin and histology

Hemangioblastomas are characterized by "stromal" lipid laden neoplastic cells within an abundant irregular reticular capillary network [56]. Similar to the embryologic hemangioblast, hemangioblastoma stromal cells express brachyury, Scl (stem cell leukemia) and Flk-1 (VEGF-R 2) [57]. Scl expression is developmentally regulated in the observed distribution of CNS hemangioblastomas in VHL patients. These findings indicate that CNS hemangioblastomas may originate from embryologic arrested-hemangioblasts. Grossly, the tumor nodule is orange-red in color (Figure 3).

Treatment

Using well-defined microsurgical techniques, the vast majority of hemangioblastomas in the CNS can be excised safely [6,8]. Most VHL patients will develop numerous hemangioblastomas growing at different rates at several locations. Because of the irregular growth pattern (including saltatory growth) and the inability to accurately predict which tumors will become symptomatic, surgical resection should be reserved until the first onset of signs/symptoms that correlate to the location of the hemangioblastoma. This surgical management paradigm avoids unnecessary surgery and can be used to maintain neurologic function in most patients [6-8].

Arteriography is sometimes used as a vascular map to better define feeding vessels before the resection of large CNS hemangioblastomas. Some surgeons will use preoperative arteriography and embolization before surgical removal of hemangioblastomas in an effort to control and reduce the tumors vascular supply [6,8]. However, we and others have found that embolization of hemangioblastomas has limited benefit and does not justify the corresponding risks associated with it [8,58,59]. Careful complete microsurgical resection can be performed with minimal blood loss without embolization [1,6,8,60].

Radiation therapy has been used for treatment of CNS hemangioblastomas in VHL. A recent study by Asthagiri and colleagues [61] demonstrated that stereotactic radiosurgery had an acceptable risk for adverse radiation effects, but had diminishing tumor control over long-term follow-up. Consequently, stereotactic radiosurgery typically used for the treating hemangioblastomas that are not surgically resectable. The use of infratentorial craniospinal radiation therapy (ICSRT) has also been investigated in VHL patients (7 patients with 84 hemangioblastomas). With long term follow-up (mean, 73.8 months), complete radiographic resolution was achieved in 18% of lesions. Over the study duration, 4 surgeries were required for treatment of symptomatic lesions after ICSRT [62].

Pharmacological treatments have been used for management of CNS hemangioblastomas. Due to the highly vascular nature of hemangioblastomas, VEGF has been a major chemotherapy target, as well as other anti-angiogenic agents. Observations of Interferonα (IFNα) in inhibiting angiogenesis have made it an intriguing target for hemangioblastoma treatment. A small scale study demonstrated that treatment with INFα did not prevent growth of visceral cysts and hemangioblastomas. Semaxanib, is an inhibitor of the Flk-1/KDR receptor tyrosine kinase (VEGR-receptor), and vatalanib, an inhibitor of VEGF-receptor tyrosine kinase, have shown promise but these agents require additional study to determine effectiveness [63]. Recent data suggest that hemangioblastomas that have a missense germline mutation may be treated with proteasome inhibitors [64].

RETINA HEMANGIOBLASTOMA

General

Retinal hemangioblastomas can occur in an estimated 60% of VHL patients and are the first symptomatic manifestation in 33% of patients. Mean age for diagnosis of retinal hemangioblastomas is 25 years, but retinal hemangioblastomas can occur as early as infancy. In fact, 5% of retinal hemangioblastomas can be found in VHL patients less than 10 years of age [1,9,10].

Natural history

Retinal hemangioblastomas are often multiple and bilateral (50%). They vary in size from less than one optic disc to several optic discs in diameter. They may arise in the peripheral retina or the juxtapapillary retina. Fifteen percent of hemangioblastomas are located at the optic disc [9,65]. Despite exhibiting slow and/or saltatory growth, they are capable of causing significant visual morbidity. Dollfus and colleagues found that the average number of hemangioblastomas observed per gene carrier with an ocular manifestation was 1.4 at initial evaluation (range, 1 to 20 hemangioblastomas) and nearly 3 (range, 1 to 20 hemangioblastomas) at final evaluation. Similar to craniospinal hemangioblastomas in VHL patients, the mean number of new hemangioblastomas per patient (of the group with ocular manifestation) per year was 0.4 [9].

Clinical features

Retinal hemangioblastomas are often asymptomatic in the initial stages. Nevertheless, they can ultimately lead to partial or total loss of vision. Symptoms correlate with the hemangioblastoma's location on the retina/optic disc. Generally, symptoms are cause by tumor exudate or tractional effects.

Ophthalmologic findings

Indirect fundoscopy and fluorescein angiography are used for diagnosis. Macular function associated with peripheral and optic nerve lesions is assessed by fluorescein angiography. Grossly, retinal hemangioblastomas are round, circumscribed, orange-red vascular associated with a feeding artery leading from the optic disc and a draining vein.

Histology and origin

Similar to other CNS hemangioblastomas, retinal hemangioblastomas are composed of vacuolated foamy cells that contain large intracytoplasmic lipid inclusions and fenestrated channels [65].

Treatment

Early diagnosis and treatment is crucial to prevent retinal detachment, hemorrhage, glaucoma, and cataracts. These complications can result in blindness in up to 25% of the affected eyes of VHL patients [9]. Treatments include laser photocoagulation, cryotherapy, photodynamic therapy, radiation or surgical excision. Location of the tumor effects treatment efficacy and applicability. Treatments for peripheral retinal hemangioblastomas cannot always safely be used for juxtapapillary hemangioblastomas. Many peripheral retinal tumors are effectively treated by laser cryotherapy or photocoagulation [66]. In cases of severe lesions with a large fibrovascular component, vitroretineal surgery has been used effectively to improve or prolong visual function [67]. Tumors located on the optic disc may be monitored,a s some treatments can cause visual damage. Enucleation may be needed in cases of irreversible glaucoma (with severe pain) with end-stage ocular angiomatosis. Finally, intravitreal injections of anti-VEGF therapeutics have been reported to reduce retinal thickening and retinal hard exudates associated with retinal hemangioblastomas that are not treatable by conventional methods (Table 3) [68].

ELSTs

General

ELSTs are vascular low-grade papillary adenocarcinomas that were identified as part of the VHL spectrum in 1997 [69]. They affect up to 11% of the individuals with VHL. Mean age of diagnosis of 22 years (range, 12 to 50 years). Bilateral ELSTs (30%) can be found in VHL [69]. ELST frequency in VHL is likely higher because many VHL patients may have an infraradiologic ELST [70].

Natural history

In one study, 31 VHL patients with ELSTs (15 males, 16 females) underwent surgical resection of their ELST at a mean age of 38.2 ± 10.2 years (range, 12-67 years). The majority of the patients (29 patients, 31 ears, 94% of ears) had associated audiovestibular symptoms, including sensorineural hearing loss (84% of ears), tinnitus (73%), and vertigo (68%) that did not correlate with tumor size [71]. Based on data from these patients and prior studies, 3 distinct mechanisms were found to underlie audivestibular findings associated with ELSTs [72]. The mechanisms include intralabyrinthine hemorrhage, endolymphatic hydrops and direct invasion of the otic capsule by tumor [73-75].

Table 3: Recommended screening and intervals of test for at-risk individuals.

Test	Start age (frequency)
Ophthalmoscopy	Infancy (yearly)
Plasma or 24 h urinary catecholamines and metanephrines	2 years of age (yearly and when blood pressure is raised)
MRI of craniospinal axis	11 years of age (yearly)
CT and MRI of internal auditory canals	Onset of symptoms (hearing loss, tinnitus, vertigo, or unexplained, difficulties of balance)
Ultrasound of abdomen	8 years of age (yearly; MRI as clinically indicated)
CT of abdomen	18 years of age or earlier if clinically indicated (yearly)
Audiological function tests	When clinically indicated

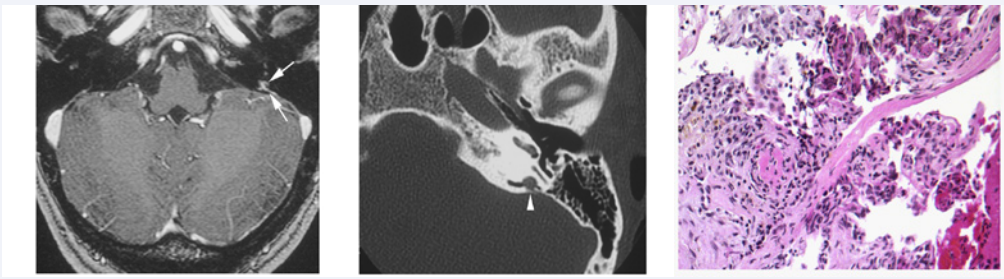

Figure 4 Imaging and histological findings from a left-sided endolymphatic sac tumor (ELST) within the vestibular aqueduct. (Left panel) Axial, T1-weighted, enhanced magnetic resonance (MR)-imaging of an ELST within the proximal vestibular aqueduct. (Middle panel) Corresponding axial, unenhanced CT imaging demonstrated tumor-associaed erosion in the vestibular aqueduct. (Right panel) Hematoxylin and eosin staining demonstrates a papillary-cystic ELST. Original magnificationX20. (Adapted from Lonser et. al. J Neurosurg, 2008) [75].

Clinical features

Because ELST patients most frequently present with a triad of findings, consisting of hearing loss, tinnitus, and vertigo, they can be misdiagnosed with Meniere's disease. Aural fullness, aural pain and facial nerve weakness are less common signs and symptoms [69]. Sudden hearing loss (43%) has been correlated with intralabyrinthine hemorrhage. Gradual hearing loss (47%), however, may be related to endolymphatic hydrops [72,74].

Radiologic findings

MR-imaging of larger ELSTs can show a homogeneous or variable pattern of patchy enhancement post-contrast. Recently efforts have been made to focus on symptomatic ELSTs below the detectable size of that seen on traditional CT or MR-imaging. Nonenhanced T1-weighted MRI has been used to reliably detect ELST-associated intralabyrinthine hemorrhage within the vestibule, cochlea, or semicircular canals distinct from the site of tumor; this may be detected prior to the tumor mass being identified on imaging. Contrast-enhanced delayed FLAIR MR-imaging has been shown to detect ELST-associated hydrops (Figure 4) [76]. Imaging studies should be supplemented with audiograms to document the extent of hearing loss in order to detect any lesions that may not be detectable my radiographical studies.

Histology and origin

ELSTs arise within the vestibular aqueduct portion of the endolymphatic duct/sac system [75]. Histologically, ELSTs are highly vascular, bright or dark red soft tissue masses that may often preferentially erode the immediately adjacent temporal bone. They often have proteinaceous papillary cystic regions [69]. ELST are immunoreactive to anti-NSE, anti-MAK6, and anti-AE1/AE3, as well as EMA and S100 in a subset of cases [Figure 4].

Treatment

Regular screening of VHL patients for ELSTs is recommended, with surgical intervention in selected patients before morbidity develops. Surgery is curative for completely excised tumors. Kim and colleagues found that hearing was stabilized postoperatively in 90% of patients after ELST resection [71]. Current indications for ELST resection in VHL include imaging evidence of an ELST with serviceable hearing (and/or audiovestibular signs/symptoms), evidence of ELST-associated intralabyrinthine hemorrhage, ELST-associated hydrops or mass effect by the ELST [74]. The role of adjuvant therapy, including chemotherapy, fractionated radiotherapy or gamma knife radiosurgery is not established.

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