Characterization of endolymphatic sac tumors and von Hippel–Lindau disease in the International Endolymphatic Sac Tumor Registry

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ABSTRACT: *Background.* Endolymphatic sac tumors (ELSTs) are, with a prevalence of up to 16%, a component of von Hippel–Lindau (VHL) disease. Data from international registries regarding heritable fraction and characteristics, germline *VHL* mutation frequency, and prevalence are lacking.

Methods. Systematic registration of ELSTs from international centers of otorhinolaryngology and from multidisciplinary VHL centers' registries was performed. Molecular genetic analyses of the *VHL* gene were offered to all patients.

Results. Our population-based registry comprised 93 patients with ELST and 1789 patients with VHL. The prevalence of *VHL* germline mutations in apparently sporadic ELSTs was 39%. The prevalence of ELSTs in patients with VHL was 3.6%. ELST was the initial manifestation in 32% of patients with VHL-ELST.

Conclusion. Prevalence of ELST in VHL disease is much lower compared to the literature. VHL-associated ELSTs can be the first presentation of the syndrome and mimic sporadic tumors, thus emphasizing the need of molecular testing in all presentations of ELST. © 2015 Wiley Periodicals, Inc. *Head Neck* **38:** 673–679, 2016

KEY WORDS: endolymphatic sac tumor, von Hippel–Lindau, prevalence, temporal bone MRI

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INTRODUCTION

Endolymphatic sac tumor (ELST), previously described as low-grade papillary adenocarcinoma of the endolymphatic sac, is a rare tumor of the inner ear. It originates from endolymphatic epithelium and arises within the intraosseous portion of the endolymphatic duct/sac of the vestibular aqueduct.[1,2] ELST is highly vascular and histopathologically characterized by papillary and glandular architecture.[3,4] Despite its categorization as a slow-growing, benign neoplasm, it is locally aggressive and invasive with infiltration of the petrous bone and destruction of the labyrinth.[4] ELSTs were first identified by Hassard et al[5] in 1984. In 1989, Heffner[6] described a series of 20 patients with papillary epithelial tumors of the temporal bone with uniform histology and destruction of the posterior wall of the petrous bone and called them "low-grade adenocarcinoma of probable endolymphatic sac origin." Before this landmark article, this entity was occasionally misdiagnosed as metastases, mainly from primary thyroid carcinomas, initiating unnecessary thyroidectomy.[4,6] These tumors occur sporadically or as a main component of the autosomal dominant von Hippel–Lindau (VHL) disease, a disorder predisposing to a variety of visceral and central nervous system (CNS) lesions, such as hemangioblastomas of the retina and CNS, pheochromocytomas, clear cell renal carcinomas, neuroendocrine pancreatic tumors, and pancreatic cystadenomas.[7–12] The diagnosis of VHL is based on specific clinical and radiological findings and on germline mutations of the *VHL* gene.[13] Typical symptoms caused by ELSTs are tinnitus (approximately 92%), vertigo and disequilibrium (approximately 62%), and sensorineural hearing loss (approximately 95%).[14–16] Significant neurological disability with important defects of the vestibulocochlear cranial nerve is common.[15,17] Sensorineural hearing loss may result in complete deafness and can occur suddenly (approximately 43%) or in a stepwise progressive manner (approximately 43%).[14–16] ELST-associated sensorineural hearing loss and vestibulopathy may occur suddenly because of tumor-associated intralabyrinthine hemorrhage or endolymphatic hydrops independent of ELST tumor size.[18]

Sensorineural hearing loss tends to develop early in life with an age-at-onset of about 22 years and is almost always irreversible.[15] At the time of diagnosis, neurological and audiovestibular defects have usually been present for several years. To avoid uncontrollable growth leading also to potentially intradural extension and brain compression, early surgery with complete resection is the treatment of choice, which may, in some cases, preserve hearing and stabilize a progressive sensorineural hearing loss.[19] ELSTs have a very young age-at-onset, a high chance of severe, irreversible, and disabling audiovestibular defects resulting in an enormous health burden for patients with VHL. The knowledge of their prevalence and clinical characteristics is important for risk management and effective preventive care. Therefore, we took a population-based registry approach to determine prevalence and clinical characteristics of ELST in patients with VHL and of VHL in patients with ELST in an international ELST registry.

MATERIALS AND METHODS

Patients

For this study on ELSTs, a consortium of otorhinolaryngologists and a consortium of specialists of VHL were established. The study included 2 approaches: to register all patients with symptomatic ELSTs and to identify patients with ELSTs in the VHL registries of the participating centers.

For the registration of symptomatic ELSTs, all departments of otorhinolaryngology of all university medical centers and large city hospitals with ENT units in Germany, France, The Netherlands, and selected centers in Italy and Spain were contacted and asked to contribute patients diagnosed with ELSTs. Nine patients from the Dutch registry were reported earlier by Timmer et al.[19]

For the identification of ELST in patients with VHL, the major centers for von Hippel–Lindau disease are Paris for France, Freiburg for Germany, Groningen, Nijmegen, Rotterdam and Utrecht for The Netherlands, Padova for Italy, Madrid for Spain, Cambridge for Great Britain, Yokohama for Japan, and Buenos Aires for Argentina. Patients with ELSTs and clinically and molecular genetically confirmed diagnoses of VHL were eligible for this study. All registrants had regular radiological examination by MRI of the brain, including the petrous bone within the inner ear. All patients underwent complete audiologic examination if symptoms for an ELST were present at the time of the MRI.

Radiological imaging

We have performed MRIs at 1.5 Tesla using a 12-channel head coil. The investigation consisted of T2w and T1w sequences without and with contrast medium. The T2w images were performed as constructive interference steady state sequence with a spatial resolution of 0.7 mm^3, and the T1w images were performed as T1weighted magnetization prepared rapid gradient echo spatial resolution of 1 mm^3. High resolution CT was added in any case in which the MRI was suspicious for an ELST and in all patients who reported experiencing hearing loss. A technique similar to the one explained above was used in all centers.

Clinical studies

All registrants provided demographic and clinical information, including sex, age at diagnosis, symptoms, surgery, postoperative morbidity, and family health histories. ELSTs were characterized by tumor number (unilateral or bilateral) and location (unilateral or bilateral). Audiovestibular defects, sensorineural hearing loss, hypacusis, in particular unilateral or bilateral deafness, were recorded. Patients with VHL-associated ELSTs underwent regular clinical screening comprising MRI of the CNS, MRI of the abdomen, and retinoscopy to identify additional VHL-specific lesions. The specific lesion at initial diagnosis, age at diagnosis of retinal angioma, hemangioblastoma of the CNS, renal cell carcinoma, pheochromocytoma, and pancreatic neuroendocrine tumors were recorded.

All operated tumors were histopathologically confirmed as ELSTs according to the criteria reviewed by Kempermann et al.[4]

TABLE 1. Clinical characteristics of the International Endolymphatic Sac Tumor registry.

	Sporadic ELSTs No. of patients = 25	VHL-associated ELSTs No. of patients = 68	*p* values
Age, y			
Mean	40	30	.002
Range	12–78	6–62	
Sex			
Female (%)	10 (40)	42 (62)	.061
Male (%)	15 (60)	26 (38)	
Symptomatic (%)	25 (100)	62 (91)	
Asymptomatic (%)	–	6 (9)	–
Bilateral (%)	–	13 (19)	
Unilateral (%)	25 (100)	55 (81)	.018
Initial ELST (%)	25 (100)	22 (32)	–
CNS hemangioblastoma (%)		49 (72)	
Retinal angioma (%)		37 (54)	–
RCC (%)	–	31 (46)	
Pheochromocytoma (%)		13 (19)	
PNET (%)		8 (12)	

Abbreviations: ELSTs, endolymphatic sac tumors; VHL, von Hippel–Lindau; CNS, central nervous system; RCC, renal cell carcinoma; PNET, pancreatic neuroectodermal tumor.

Molecular genetic analyses

All research participants were asked to provide 10 mL EDTA-anticoagulated blood for molecular genetic studies. Screening for germline point mutations, small deletions, and insertions in the 3 exons and splice sites of the *VHL* gene (NM_000551.2) was performed. Briefly, germline DNA was extracted from peripheral leukocytes under standard procedures and the screening was performed by direct Sanger sequencing. Screening for large deletions of the *VHL* gene was performed using the commercially available MLPA kit (MRC Holland).[20–22]

Statistical analyses

Data collection and analyses were performed with IBM SPSS version 21 (SPSS, Chicago, IL). Scale and categorical data were expressed as median and range, absolute and relative frequencies, respectively, and statistical testing of observed differences performed by 2-sided Mann–Whitney and chi-square test at a significance level of $p = .05$. Calculation of a confidence interval for a proportion was done with MedCalc 14.8.1 (MedCalc Software bvba). Age-specific cumulative incidence was estimated and plotted by the Kaplan–Meier method, and the 2-sided log-rank test used for statistical testing of observed differences. Kaplan–Meier plots were performed with MedCalc 14.8.1.

Approval and consent

The study design was approved by the ethical committee of the University of Freiburg and all participating centers, accordingly. All participants gave written informed consent. The study was performed in accordance with the guidelines of the Helsinki Declaration of 1975, as revised in 1983.

RESULTS

The International Endolymphatic Sac Tumor Registry

As of July 2014, the international ELST registry was comprised of 93 registrants (52 women and 41 men). Age at diagnosis was 6 to 78 years (median, 31 years). Of the 93 registrants, 37 were French, 29 were German, 11 were Dutch, 6 were Italian, 4 were Spanish, 3 were British, 2 were Japanese, and 1 was Argentinian.

Among the 93 ELST registrants, 52 (56%) presented with the characteristic clinical features of VHL disease, with hemangioblastoma of the retina or the CNS, renal cell carcinoma, pancreatic cysts or neuroendocrine pancreatic tumor, and/or pheochromocytoma or had a positive family history.

Forty-one registrants (44%), registered from Germany, France, Italy, Spain, and The Netherlands, presented with apparently sporadic ELST. Among these 41, 16 (39%) were found to have a *VHL* germline mutation. Thus, 25 patients had truly sporadic ELSTs. Overall, 68 registrants had VHL-associated ELST. Of these 68 patients, 22 (32%) first presented with ELST.

The VHL registries in France, Germany, Italy, The Netherlands, Japan, Spain, and Argentina consisted of 599, 593, 229, 157, 42, 88, and 81 patients, respectively, resulting in a total of 1789 patients, all of whom underwent cranial MRI. Among these countries, a total of 65 patients were found to have VHL-associated ELST. Thus, the prevalence of ELSTs in VHL was 5.0% (30 of 599) in France, 3.4% (20 of 593) in Germany, 2.3 (6 of 229) in Italy, 2.0% (3 of 157) in The Netherlands, 4.7% (2 of 42) in Japan, 3.4% (3 of 88) in Spain, and 1.2% (1 of 81) in Argentina. This results in an overall prevalence of 3.6% (65 of 1789).

Sporadic versus von Hippel-Lindau–associated endolymphatic sac tumors

In our registry, VHL-associated ELSTs were seen more frequently than sporadic ELSTs (68 vs 25; Table 1). Patients with sporadic ELST were registered from Germany ($n = 9$), France ($n = 7$), The Netherlands ($n = 8$), and Spain ($n = 1$), whereas patients with VHL-associated ELST were registered in France ($n = 30$), Germany ($n = 20$), Italy ($n = 6$), The Netherlands ($n = 3$), Great

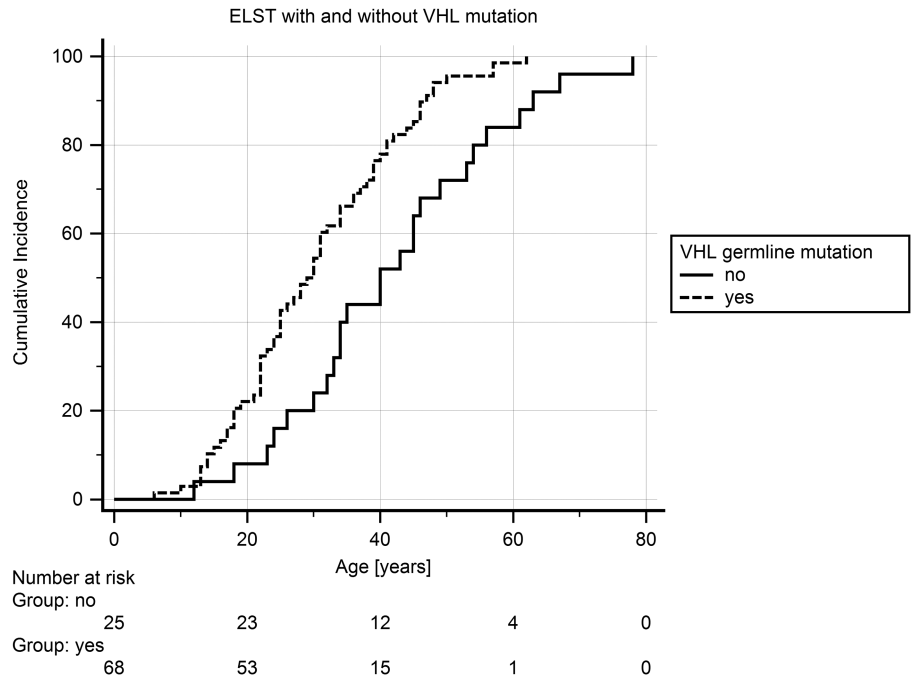

FIGURE 1. Cumulative age distribution of sporadic and hereditary endolymphatic sac tumors (ELSTs). Our population-based registry comprised 93 patients with ELST. Twenty-five patients had truly sporadic and 68 had von Hippel-Lindau (VHL)-associated ELSTs. Both sporadic and VHL-associated ELSTs presented mainly in adulthood. VHL-associated ELSTs occurred at a significantly younger age than sporadic ones with a median age at onset of 29 versus 40 years (estimated and plotted with the Kaplan–Meier method 29 vs 40 years, expressed with the 2-sided Mann–Whitney test 30 vs 40 years).

Britain ($n = 3$), Spain ($n = 3$), Japan ($n = 2$), and Argentina ($n = 1$).

Both sporadic and VHL-associated ELSTs presented mainly in adulthood (24 of 25 vs 57 of 68, respectively). However, VHL-associated ELSTs occurred at a significantly younger age than sporadic ones with a median age at onset of 30 versus 40 years ($p = .002$; Table 1; Figure 1). Both sexes were affected, although there was a trend to female predominance in VHL-associated ELST (female sporadic 10 of 25 vs VHL 42 of 68; $p = .061$). Asymptomatic ELSTs were only detected in patients with VHL by regular follow-up imaging using cranial MRI (6 of 68; 9%). All patients with sporadic ELST had unilateral tumors, whereas VHL-associated ELSTs occurred bilaterally in 19% (13 of 68). Surgery with complete resection of the tumors was the standard of care in all sporadic ELSTs. In contrast, only 58 of 68 patients (85%) with VHL-associated ELSTs underwent operations for their tumor.

A total of 4 patients (4%) died, 1 with sporadic ELST and 3 with VHL-associated ELSTs. The causes of death were not associated with ELSTs.

von Hippel-Lindau-associated endolymphatic sac tumors

There was a total of 68 patients had VHL-associated ELSTs. Of these 68, 62% had a positive and 38% had a negative family history for tumors in the spectrum of the VHL syndrome. ELSTs were the initial presentation in 22 VHL-ELST registrants (32%; Table 1). Hemangioblastoma of the CNS and the retina were present initially or during follow-up in 59 patients (87%). Thirteen of the 68 patients (19%) presented with a pheochromocytoma and 31 (46%) with a renal cell carcinoma. Pancreatic lesions were present in 41 patients, of which 8 were neuroendocrine pancreatic tumors (12%), 1 was a cystadenoma and 35 were multiple cysts (Table 1).

VHL germline mutations were known for 64 of the 68 patients with VHL (Table 2). The mutation spectrum of the patients with VHL-associated ELSTs is broad: 30 (47%) were missense mutations, 14 (22%) were large deletions, 12 (18%) were nonsense, 5 (8%) were small intra-exonic deletions, and 3 (5%) were splice-site mutations, but not significantly different from that of VHL cases without ELST. About half of ELST-associated *VHL* germline mutations resulted in a truncated protein and loss of protein function. Median age at diagnosis of ELST was 28 years in patients with truncating mutations compared to 31 years in those with nontruncating mutations ($p = .47$). There was no significant difference for bilateral ELST tumors between these 2 mutation groups ($p = .093$).

DISCUSSION

In this study, to the best of our knowledge, we present the largest and the first population-based, international study on ELSTs comprising 93 such patients. Our study sought to address 3 questions: (1) how frequent is VHL in patients who primarily present with symptomatic ELST; (2) how frequent are ELSTs in VHL; and (3) are there clinical differences between sporadic and VHL-associated ELSTs. These questions are of great importance for patients with VHL as well as all presentations of ELSTs and management guidelines of the various specialists who have to care for these patients.

Prevalence of endolymphatic sac tumors in von Hippel-Lindau

The international ELST registry contains 93 registrants. Among these 93, 41 registrants had apparently sporadic

TABLE 2. Germline mutation spectrum of von Hippel–Lindau-associated endolymphatic sac tumors.

No. of registrants	Country	Nucleotide position (NM_000551.3)	Predicted effect on protein
1	France	c.197_209del	p.Val66Glyfs*89
4	Germany France	c.226_228delTTC	p.Phe76del
2	Germany Japan	c.233A>G	p.Asn78Ser
1	Germany	c.236_241delGCAGTC	p.Arg79_Ser80del
1	Italy	c.256C>G	p.Pro86Ala
1	France	c.256C>T	p.Pro86Ser
1	France	c.266T>C	p.Leu89Pro
1	France	c.275A>G	p.Asp92Gly
1	Germany	c.292T>C	p.Tyr98His
1	France	c.331A>T	p.Ser111Cys
2	UK	c.332G>A	p.Ser111Asn
1	France	c.337C>T	p.Arg113*
1	Germany	c.339delA	p.Gly114Valfs*45
1	France	c.345C>G	p.His115Gln
1	Italy	c.358A>G	p.Arg120Gly
1	Germany	c.392A>C	p.Asn131Thr
1	France	c.397delA	p.Thr133Leufs*26
1	Spain	c.404T>A	p.Leu135*
2	Germany	c.461C>T	p.Pro154Leu
2	Germany	c.463+2T>C	splice
1	Spain	c.464-2G>A	splice
1	Italy	c.470C>T	p.Thr157Ile
1	France	c.473T>C	p.Leu158Pro
3	France Argentina	c.481C>T	p.Arg161*
1	France	c.485G>A	p.Cys162Tyr
2	France	c.486C>G	p.Cys162Trp
1	Germany	c.491A>T	p.Gln164Leu
3	France UK Germany	c.499C>T	p.Arg167Trp
4	France Italy	c.500G>A	p.Arg167Gln
1	France	c.500G>C	p.Arg167Pro
1	France	c.525C>A	p.Tyr175*
1	France	c.525C>G	p.Tyr175*
1	France	c.532T>C	p.Leu178Pro
1	France	c.533T>C	p.Leu178Pro
2	France	c.583C>T	p.Gln195*
1	Netherlands	delEx1	
1	France	delEx2	
4	France Germany Italy	delEx3	
1	Germany	delEx2–3	
6	France Germany Netherlands Spain	delEx1–3	

and 52 had VHL-associated ELSTs. Furthermore, nearly 1800 patients with VHL disease, registered in specific VHL registries in Europe, South America, and Asia, were screened for ELSTs.

In contrast to the reported prevalence of ELST in VHL disease of up to 16%, our population-based study revealed a 3.6% prevalence of ELST in VHL, considerably lower than the published literature.[12,14,15] Although small and microscopic, ELSTs could not be completely excluded by negative imaging, however, an underestimation is unlikely because we performed an MRI as recommended as an acceptable standard in our field.[23] Furthermore, the figure in the literature is almost certainly derived from tertiary referral. Whereas the prevalence figures from tertiary referral studies are important, they almost always represent the upper estimate. Because our prevalence data for ELST in VHL are far beyond the reported, the physical and psychological burden for patients with VHL is expected to decrease.

Prevalence of von Hippel-Lindau in apparently sporadic endolymphatic sac tumors

The prevalence of *VHL* germline mutations in apparently sporadic ELSTs is unknown, because the existing data are based on low case numbers.[11,19,24–32] The prevalence of *VHL* germline mutations in sporadic ELSTs in our registry is 39%. Because of the high prevalence of VHL in all presentations of ELST, it is important that all patients with ELST are screened for germline mutations in the *VHL* gene. It is standard of care in clinical cancer genetics to offer germline genetic analysis when the prevalence of germline mutation is >10%. The first such example is for medullary thyroid carcinomas, in which 10% to 25% of all apparently sporadic presentations harbor germline *RET* mutations, making the diagnosis of multiple endocrine neoplasia type 2.[33]

Endolymphatic sac tumors can be first presentations of von Hippel-Lindau

Because of the above-mentioned lack of a larger cohort of patients with sporadic ELSTs, we were able to confirm and emphasize the tendency of reported characteristics and differences of sporadic and VHL-associated ELSTs by published reviews of the literature. Patients with VHL-associated ELSTs were younger than patients with sporadic ELSTs. However, in our study, patients with VHL-associated ELSTs were older than expected with a median 30 years at presentation; instead of the given 22 years found in the literature.[15] Almost all patients with ELSTs, independent of mutation status, were symptomatic. Although bilateral occurrence of ELST is a strong indicator for VHL-associated disease, this only represented 19% in our registry compared to up to 30%.[15,17] Importantly, 32% of all our patients with VHL-ELST presented with ELST as the first symptom heralding VHL. Thus, all ELST presentations should be referred to genetics professionals for evaluation of unsuspected VHL.

Why it is important to identify von Hippel-Lindau among endolymphatic sac tumors and to identify endolymphatic sac tumors in patients with von Hippel-Lindau

Our data revealed a 39% prevalence of *VHL* germline mutations among sporadic ELSTs; similarly, a prevalence of 3% to 16% of ELSTs occurred in patients with VHL, and ELST can be the first manifestation of VHL disease in over one third of patients with VHL. These observations underscore the importance of early diagnosis of VHL-associated ELSTs, preferably with *VHL* germline mutation analysis in all apparently sporadic ELSTs cases and regular surveillance for patients with VHL. Because there are no specific genotype-ELST correlations, it would seem that any given mutation of the *VHL* gene can predispose to ELSTs. Therefore, all patients with VHL should have regular clinical screening for ELSTs. VHL is an autosomal dominant disorder and, in addition to ELST, predisposes to a variety of visceral and CNS neoplasias, such as hemangioblastomas of the CNS and the retina, pheochromocytomas, renal cell tumors, and neuroendocrine pancreatic tumors.[7–12] Thus, finding VHL in a patient with ELST would enable routine high-risk surveillance for all neoplasias of VHL disease with the possibility of an increase in life expectancy and an improvement in quality of life, the major goals of an effective preventive medicine strategy.

Equally important is the possibility of a curative complete tumor resection and preservation of hearing acuity, which is crucial in these patients, especially considering the combined additional deficiencies of vision loss and gait disturbances and their immense impact on quality of life. Additionally, identifying VHL disease offers the possibility of early detection of asymptomatic mutation carriers in the setting of genetic counseling. Patients with VHL disease should undergo age-related surveillance protocols throughout their life. A thorough physical and audiology assessment, the measurement of 24-hour urinary metanephrines or plasma metanephrines, a regular retinal investigation by ophthalmoscopy, and the performance of an MRI of the abdomen and CNS with attention to the inner ear and petrous bone are the cornerstones of an interdisciplinary diagnostic protocol. Given that, neoplasias because of genetic predisposition occur at an earlier age, not being able to proactively screen typically results in advanced disease and often unresectable disease. The latter are costly both in life-years, societal costs, and true costs, all of which can be mitigated by identifying *VHL* gene carrier status and beginning prospective clinical surveillance.

Once the diagnosis of VHL has been established, contrast-enhanced MRI of the petrous bone must be part of surveillance with yearly recommended checkups. The costs do not exceed those of a "normal" MRI of the brain. In any case, with evidence or suspicion for an ELST, surgeons specialized in operations of the inner ear have to be involved. This is a unique strategy for early recognition of ELSTs. Any detected ELST should be removed whenever possible for curative intent and to prevent deafness.

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