von Hippel-Lindau disease: Surveillance strategy for endolymphatic sac tumors

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Purpose: Up to 16% of patients with the hereditary von Hippel-Lindau disease develop endolymphatic sac tumors of the inner ear. Early diagnosis and treatment of endolymphatic sac tumors can prevent audiovestibular morbidity, but optimal endolymphatic sac tumor surveillance strategy has yet to be determined. We aimed to evaluate endolymphatic sac tumor surveillance to determine the best surveillance strategy. **Methods:** In a national prospective study, 40 *VHL* mutation carriers were interviewed about audiovestibular symptoms and had audiological examinations and magnetic resonance imaging of the inner ear. Further, we performed a meta-analysis including all reported endolymphatic sac tumor von Hippel-Lindau disease cases in the literature ($N = 140$ with 156 endolymphatic sac tumors). **Results:** In the prospective study, endolymphatic sac tumors were suspected based on audiovestibular symptoms, audiometry, and magnetic resonance imaging in 34%, 30%, and 12.5% of subjects, respectively. In total, more than 90% of radiologically diagnosed endolymphatic sac tumors were associated with abnormal audiometric findings. No endolymphatic sac tumor genotype-phenotype correlations were found. **Conclusion:** We recommend annual audiometry as a first-line endolymphatic sac tumor screening tool, and in countries where periodic surveillance magnetic resonance imaging of the central nervous system is performed, specific images of the inner ear should be included. Audiometric abnormalities in patients with von Hippel-Lindau disease without magnetic resonance imaging-visible endolymphatic sac tumors could be due to microscopic endolymphatic sac tumors. Determination of audiometric endolymphatic sac tumor characteristics could further target screening and improve endolymphatic sac tumor diagnosis. ***Genet Med*** **2011:13(12):1032–1041.**

Key Words: *clinical genetics, endolymphatic sac tumor (ELST), genotype-phenotype correlation, surveillance, von Hippel-Lindau disease (vHL)*

Endolymphatic sac tumors (ELSTs) are locally aggressive tumors of the petrous bone (Fig. 1), which can lead to severe and irreversible hearing loss and other audiovestibular and neurologic symptoms.[1] ELSTs rarely occur in the general population but have been found in up to 16% of patients with the hereditary multisystemic von Hippel-Lindau disease (vHL) (OMIM#: 193300).[1,2] vHL is caused by inactivation of the tumor suppressor gene *VHL*, and affected individuals are especially predisposed to development of hemangioblastomas in the central nervous system and retina, renal clear cell carcinoma, renal and pancreatic cysts, and pheochromocytomas. vHL manifestations can lead to severe disability and mortality, which can to some degree be prevented by prophylactic surveillance and early manifestation treatment.[3] Prevention of particularly audiovestibular morbidity due to ELSTs is crucial for vHL patients, who are also at risk of blindness and balance impairment due to retinal and cerebellar hemangioblastomas. Early diagnosis of ELSTs is essential because surgical excision of tumors can preserve the preoperative hearing level and eliminate most other audiovestibular symptoms.[1,2,4–8]

Although the association between ELST and vHL was first established by Manski et al.[1] in 1997 and several case reports have been published,[4–38] only a few studies have included more than four vHL patients with an ELST.[1,2,39,40] To date, there is no evidence as to what is the optimal strategy for ELST surveillance in vHL patients, and no uniform international guidelines exist. Magnetic resonance imaging (MRI) of the inner ear is considered the gold standard in ELST diagnosis and is typically required in surgical planning.[1,4,7,12,39] Many institutions perform regular surveillance MRI of the central nervous system in vHL patients, but unfortunately, MRI is expensive and is not easily accessible at regular intervals all over the world. Cheaper methods such as interviews about subjective audiovestibular symptoms or audiological examinations have been proposed as first-line screening tools to identify high-risk patients who should have a diagnostic MRI.[1,28,41]

Genotype-phenotype correlations have given rise to a subclassification of vHL into vHL type 1 without pheochromocytoma, predominately caused by mutations truncating the protein product of *VHL*, and vHL type 2 with pheochromocytoma, mainly caused by missense mutations.[3] It has been hypothesized that correlations between ELSTs and certain genotypes can be used to identify high-risk families for ELST development and target screening, but previous studies have been too small to demonstrate such a correlation.[1,2,34,37]

The overall objective of this study was to evaluate ELST surveillance and determine a practical first-line screening approach based on a prospective national study of *VHL* mutation carriers and a meta-analysis of all published cases and cohorts of vHL patients with ELST.

MATERIALS AND METHODS

The prospective study

In this national study, we initially included 41 *VHL* mutation carriers older than 15 years: 21 females and 20 males from 19

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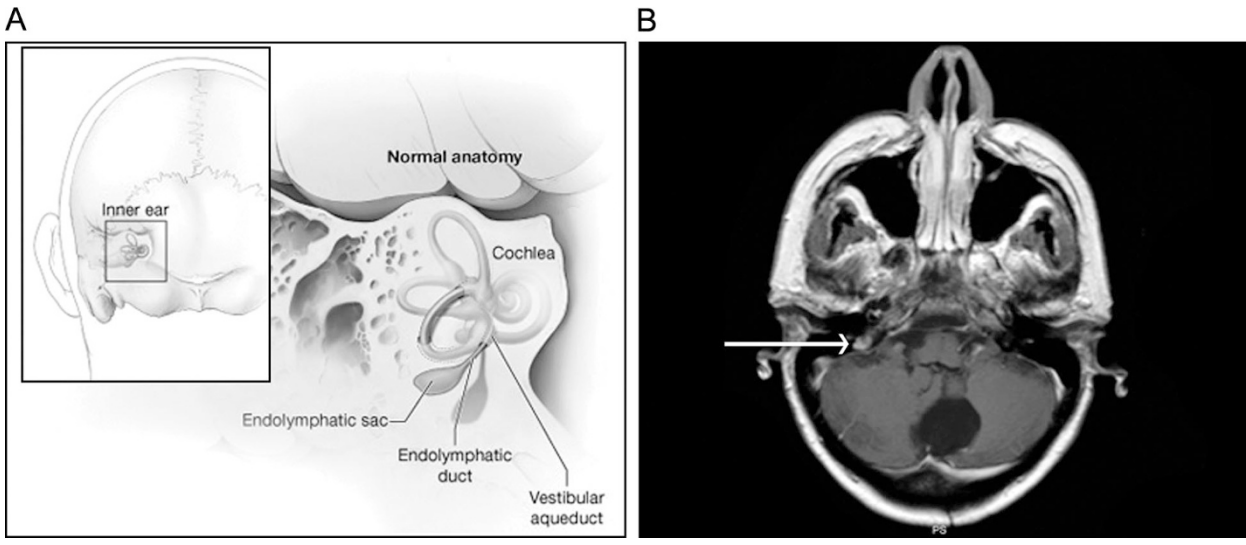

Fig. 1. Endolymphatic sac tumor. A, Anatomic location of the endolymphatic sac. B, Subject 1: contrast enhanced T1-weighted MRI image of a right-sided endolymphatic sac tumor (arrow).

unrelated vHL families, comprising 90% of all known living adult Danish *VHL* mutation carriers. Subjects and their clinical features have previously been described.[42] All subjects were systematically referred to (1) interview about ELST-related symptoms, (2) audiological examination, and (3) MRI of the inner ear. In cases where an ELST was detected on MRI, all available earlier MRIs of the brain and inner ear were retrospectively assessed to identify first signs of the ELST. One patient died during the study period and was excluded. Of the 40 remaining subjects, 36 underwent both the interview, MRI of the inner ear, and the audiological examination. Three subjects did not have an audiological examination and two did not complete an interview due to worsening of other vHL manifestations (3/4) and of unknown cause (1/4). Median age at the first study examination was 39 years (range: 15–65 years), and median interval between audiological examination and MRI was 2 months (range: 1–18 months).

Interview about subjective audiovestibular symptoms

Subjects were interviewed about subjective symptoms of hearing loss, tinnitus, aural fullness, ear pain, dizziness, and balance disturbances. Reported audiovestibular symptoms that clearly could be attributed to irrelevant causes (e.g., ear trauma, brain surgery, and noise exposure) were disregarded.

Audiological examination

The audiological examinations comprised otoscopy, pure tone audiometry (air and bone conduction thresholds), tympanometry, and determination of stapedial reflex thresholds. Speech reception thresholds and discrimination loss were determined by the standardized speech material "Dantale."[43]

MRI of the inner ear

The majority of MRIs of the inner ear (31/40) were carried out at the Danish National Hospital in Copenhagen using a 3T Siemens Magnetom TrioTim syngo B17 scanner with high-resolution MRI scanning of the brain, the 8th cranial nerve and inner ear. T1-weighted images were obtained before and after contrast media (MultiHance 0.1 mmol/kg) using a 3D magnetization preparation with rapid imaging sequence (repetition time [TR] = 2250 milliseconds/echo time [TE] = 2.94 milliseconds/inversion time = 900 milliseconds) with 1 mm isotropic resolution. Coronal T2-weighted FLAIR (TR = 9000 milliseconds/TE = 57 milliseconds/inversion time = 2500 milliseconds) and axial T2-weighted blade turbo spin echo (TR = 5500 milliseconds/TE = 113 milliseconds) images of the whole brain were acquired with 4 and 5 mm slice thickness, respectively. 3D T2-weighted turbo spin echo images (TR = 750 milliseconds/TE = 114 milliseconds) were acquired of the 8th cranial nerve, inner ear, and endolymphatic sac with 0.6 mm isotropic resolution. The MRIs that were not carried out at the Danish National Hospital in Copenhagen and those that were retrospectively reviewed for earlier ELST signs did not fulfill the described protocol of inner ear. These MRIs were predominantly axial T1 weighted obtained before and after contrast media and axial T2 weighted (both matrix = 2562 and FOV = 25 × 25 cm), both with 5 mm slice thickness.

Data assessment

All imaging data were collected and described by the same senior radiology specialist (C.T.) who identified the endolymphatic duct and sac on the 3D T1- and T2-weighted images and reported tumors and contrast enhancement. The audiological data were analyzed by the same senior ear-nose-throat specialist (S.G.) for signs of cochlear or retrocochlear pathology, with particular attention to interaural asymmetry and the configuration of the audiograms to assess whether an ELST could be suspected.

The meta-analysis

Through a review of the literature, we identified clinical descriptions of 135 additional vHL patients who were diagnosed with at least one radiologic confirmed ELST. The Pub Med database was searched for publications in English using combinations of the search words "ELST"/"Endolymphatic sac tumor/tumour" and "vHL"/"von Hippel-Lindau disease," assessing all resulting papers and related papers published since 1993 when ELST was first described as a disease entity.[44] Also, publications of vHL populations were reviewed and those containing patients with an ELST selected. Information of each

Table 1 Results of interviews, audiometries, and MRIs of the inner ear ($N = 40$)

Subject number	Subjective symptoms[a]	ELST suspicion based on audiometry	ELST on MRI
1	Yes	Bilateral	Unilateral, right sided
2	None	None	Unilateral, left sided
3	Yes	Bilateral	Unilateral, left sided
4	Yes	Unilateral, right sided	Unilateral, right sided
5	None	Bilateral	Unilateral, right sided
6	Yes	Bilateral	None
7	Yes	None	None
8	Yes	None	None
9	Yes	None	None
10	Yes	None	None
11	Yes	None	None
12	Yes	None	None
13	Yes	None	None
14	Yes	None	None
15	Yes	None	None
16	None	Bilateral	None
17	None	Unilateral, right sided	None
18	None	Unilateral, left sided	None
19	None	Bilateral	None
20	None	Unilateral, right sided	None
21	None	None	None
22	None	None	None
23	None	None	None
24	None	None	None
25	None	None	None
26	None	None	None
27	None	None	None
28	None	None	None
29	None	None	None
30	None	None	None
31	None	None	None
32	None	None	None
33	None	None	None
34	None	None	None
35	None	None	None
36	None	None	None
37	—	Bilateral	None
38	—	—	None
39	None	—	None
40	None	—	None
Total (% of subjects examined)	Yes: 13/38 (34%)	11/37 (30%) 18/74 ears (24%)	Yes: 5/40 (12.5%) 5/80 ears (6.25%)

[a]Subjective symptoms in the form of hearing loss, tinnitus, aural fullness, ear pain, and other ear problems. (Results of questions of sensation of dizziness and balance problems are not included, because in 100% [13/13] and 88% [14/16] of subjects who reported dizziness and balance problems, respectively, these symptoms were clearly attributed to previous brain surgery of cerebellar hemangioblastomas).
—, no examination done for this patient.

ELST patient's age at diagnosis, audiovestibular symptoms, audiological examinations, symptom duration, type of *VHL* germline mutation, and vHL phenotype were extracted, pooled, and evaluated.

Ethics

The study was approved by the Danish Regional Committees on Biomedical Research Ethics and the Danish Data Protection Agency. All subjects in the prospective study gave their oral and written consent to participation.

RESULTS

The prospective study

Table 1 lists details of interviews, audiological examinations, and MRIs for all subjects, whereas Table 2 lists characteristics of subjects with an MRI-diagnosed ELST.

The overall occurrence of MRI-diagnosed ELSTs in this study population was 12.5% (5/40 subjects). Overall, 34% (13/38) of subjects reported subjective audiovestibular symptoms, and of these, three (23%) also had ELST suspect audiograms, and four (31%) were found to have MRI-visible ELSTs. Four of the five subjects with an MRI-diagnosed ELST had an ELST suspect audiometry, and three of these also reported subjective audiovestibular symptoms. Apart from the audiometric results, nothing further could be concluded based on the other test parameters of the audiological examination.

A retrospective review of the five ELST subjects' earlier MRIs, on which no ELSTs had previously been diagnosed, revealed that in two subjects the lesions could be seen 16.5 months and 51.5 months before ELST diagnosis, respectively. Neither of these two lesions had been acknowledged before this investigation even though both patients had undergone 3 and 2 MRIs, respectively. These two ELSTs were surgically removed, and histology confirmed one to be an ELST but revealed that the other was a hemangioblastoma. The subject with the hemangioblastoma that had been mistaken for an ELST radiologically (Subject 2 in Tables 1 and 2) had unremarkable audiometric findings and did not report any subjective audiovestibular symptoms.

Table 2 Characteristics of subjects diagnosed with ELST

Subjects	Age and gender	Subjective audiovestibular symptoms	Audiometric characteristics of ELST	MRI characteristics: Size and location of ELST at diagnosis	MRI characteristics: Period of retrospective ELST identification (Period evaluated)[a]	Histology	Other vHL manifestations: CNS Hbs	Retinal Hbs	RCC	Pheo	Renal cysts	Pancreas cysts	Epi cysts
1	47-year-old woman	Tinnitus, hearing loss, disturbed sound perception, spells of dizziness	Right side: hearing loss at all frequencies	12.0 × 11.0 mm, Right sided	16.5 months (36.5 months)	ELST	X	X			X	X	
2	41-year-old man	None	None	6.0 × 10.0 mm, Left sided	51.5 months (51.5 months)	Cerebellar hemangioblastoma	X	X	X		X	X	
3	55-year-old man	Hearing loss	Left side: low frequency hearing loss	2.0 × 2.0 mm, Left sided	0 months (129 months)	Not operated	X				X		
4	41-year-old man	Tinnitus	Right side: low-frequency hearing loss	1.4 × 1.4 mm, Right sided	0 months (84 months)	Not operated	X				X		X
5	30-year-old man	None	Right side: low frequency hearing loss	1.4 × 4.0 mm, Right sided	No prior MRIs available	Not operated		X	X		X		

[a]Number of months before ELST diagnosis, where the ELST could retrospectively be identified on prior MRIs of the cerebrum (number of months retrospectively evaluated).
Hbs, hemangioblastomas; RCC, renal clear cell carcinoma; Pheo, pheochromocytomas; epi cysts, epididymal cystadenomas (men)/cysts of the broad uterine ligament (women).

The meta-analysis

Overall, 140 vHL patients with 156 radiologic confirmed ELSTs were identified in the literature and our prospective study (Table 3).

Approximately 11% (16/140) were reported to have bilateral ELSTs. Approximately 96% had at least one audiovestibular symptom at the time of ELST diagnosis. Among these, sensorineural hearing loss was found in 91% ($N = 82/90$), tinnitus in 64% ($N = 58/90$), vertigo in 52% ($N = 47/90$), disequilibrium in 18% ($N = 16/90$), sensation of aural fullness in 14% ($N = 13/90$), aural pain in 4% ($N = 4/90$), and facial nerve paresis in 8% ($N = 7/90$).[1,2,4–15,18–28,30–34,37,40,45,46] The median time from subjective onset of symptoms, including cases with sudden onset, to ELST diagnosis was 3 years (range: 0 to >20 years, $N = 26$), and 27% of these patients (7/26) reported to have had subjective symptoms for more than 10 years.

Information from patients' audiological examinations was available for 102 ears with radiologically visible ELSTs, and 92% (94/102 ears) were described as being abnormal. Detailed information of audiometric patterns was given for 18 ears with ELSTs in the combined prospective study and meta-analysis.[4–7,11] A distinct low-frequency hearing loss was described in 8 of these 18 ears, including three ears in the prospective study.[4,6,7] In seven of the eight cases, audiograms were available for evaluation, demonstrating that the low-frequency hearing loss was exclusive, not involving frequencies above 1000 Hz. Tumor sizes were reported in six of the eight ELSTs associated with low-frequency hearing loss, and mean diameter was 2.5 mm (range: 1.4–11 mm).[4,6,7] The remaining nine ELST ears with audiometric details showed various patterns, predominately severe to profound sensorineural hearing loss of all frequencies. Tumor size was only reported for two of these tumors, which were 2 mm and 12 mm in diameter, respectively.

DISCUSSION

We present the first systematic evaluation of ELST surveillance in the largest collective population of patients with vHL and ELST presented to date, based on a prospective national study including 90% of all known *VHL* mutation carriers in Denmark, and a meta-analysis of all reported patients with vHL and ELST in the literature since 1993. Our results indicate that annual audiometry is suitable as a first-line ELST screening tool among patients with vHL, especially in countries where surveillance MRIs are inaccessible. In countries where routine MRI of the central nervous system is performed every 12–36 months as part of a vHL surveillance program, the inner ear may be included in these examinations.

Based on the present findings, the use of subjective audiovestibular symptoms alone to target ELST screening is a too insensitive and unspecific approach, because these symptoms represent a broad and unspecific spectrum of symptoms. Further, it has been demonstrated that neither severity nor duration of audiovestibular symptoms are associated with radiologically determined tumor size[39] and that there is no difference in the incidence of subjective hearing loss or tinnitus in vHL patients without radiologic ELST signs compared with their family members without vHL.[2] Even though there was a high frequency of subjective symptoms of approximately 35% among subjects in the prospective study, almost 70% (9/13 subjects) of these subjects showed no ELST signs on either MRI or audiological examination. Furthermore, ELSTs are not always subjectively symptomatic at diagnosis as also seen in the prospective study.[1,4,6,39] The high frequency of almost 100% of subjective audiovestibular symptoms before ELST diagnosis found in the meta-analysis might reflect bias in the included studies. Most studies identified patients unsystematically, and some patients may have been selected because of audiovestibular symptoms, rendering a group not representative of the general vHL population. This notion is supported by the long period of time from symptom onset to ELST diagnosis found in the meta-analysis where more than a fourth of ELST patients had audiovestibular symptoms for more than 10 years before an ELST was diagnosed.

Audiometry seems to be a good first-line screening tool in ELST surveillance for vHL patients. More than 90% of vHL patients with radiologically diagnosed ELSTs had abnormal audiometric findings when including only the studies reporting audiological parameters in the combined meta-analysis and prospective study.[1,2,4,5,7,11,16,17,39] These results might be influenced by publication bias, because the three largest studies in the meta-analysis, overall accounting for 77 of the ELST ears with audiological data, were all from the same institution, without information of whether the same patients were included in more than one of the three series.[1,2,39] Based on present results, use of audiometry seems to be more cost-effective than use of a full audiological examination, as audiometry alone is simpler to perform, and as we found no further ELST indicators based on the rest of test parameters in the full audiological examination.

In ELST patients with hearing loss, subjective symptom onset was described as being sudden in approximately half of patients and progressive in the other half.[2,39] Based on the combined prospective study and meta-analysis, the development of progressive hearing loss seems to correlate with a characteristic audiological pattern.[4–7,11] A distinct and exclusive low-frequency hearing loss was reported in almost half of ELST cases (8/18 ears) in which detailed audiologic data were available, and all were small ELSTs (mean diameter 2.5 mm). Larger ELSTs are described to cause profound sensorineural hearing loss involving all frequencies, yielding a flat audiometric curve.[5,6] The mechanism for the sudden onset of hearing loss is described by Butman et al.[39] to be tumor-associated intralabyrinthine hemorrhaging and can occur in even the smallest ELSTs. It is, however, not known whether ELST patients with sudden onset of hearing loss have had audiometric signs of a yet asymptomatic ELST before subjective symptom debut.

In the future, audiometry might be able to diagnose early-stage ELSTs before they can be seen on MRI. Audiovestibular symptoms and audiometric suspicion of ELSTs have been described to precede the visualization of ELSTs on MRI.[4,47] In the prospective study, only two of the five subjects with an ELST had had both an audiological examination and MRIs of the inner ear before the study, and one of these subjects did have audiometric documented hearing loss 2 years before an ELST could be identified. Furthermore, almost 20% (14/74) of ears in the prospective study had audiometric suspicion of ELST without having MRI-visible ELSTs. Manski et al.[1] also found an even higher incidence of almost 60% (29/49) with audiometric abnormalities among vHL patients without ELST imaging evidence. It cannot be excluded that these audiometric abnormalities are caused by microscopic ELSTs. Nevertheless, audiometry indicative of ELST without radiologic evidence does not warrant surgical intervention at this point, and better knowledge of clinical and audiometric patterns of ELSTs is needed. For this purpose, we have recently initiated an international collaborative study of audiological data and radiologic imaging in vHL patients with and without ELST

Table 3 Cases of ELST in vHL patients reported in the literature

N	Age at ELST diagnosis[a] (yr)	Symptoms at diagnosis (*N*)[b]	No. ears with abnormal audiological examination of ears examined	Germline *VHL* mutation(s)[c]	Mutation consequence[d]		vHL type (*N*)[e]		Studies
					Truncated protein	Missense mutation	Type 1	Type 2	
1	20	1	NR	NR	NR	NR	1	0	9
1	29	1	NR	NR	NR	NR	1	0	10
1	48	1	NR	NR	NR	NR	1	0	12
1	28	1	NR	NR	NR	NR	NR	NR	13
13	Mean: 22 (range: 12–50)[f]	13	15 of 15	7 mutation carriers of 10 subjects tested: 4 large deletions and *c.430C>T, c.769G>T, c.553G>C*	6	1	6	4	1
1	22	1	NR	NR	NR	NR	1	0	14
1	25	1	NR	NR	NR	NR	1	0	15
1	32	1	1 of 1	3-nucleotide insertion within exon 2	1	0	0	1	16
1	22	NR	1 of 1	1-base deletion of exon 1 at nucleotide 930	1	0	1	0	17
1	54	1	NR	NR	NR	NR	NR	NR	18
1	17	1	NR	NR	NR	NR	1	0	19
1	34	1	NR	NR	NR	NR	1	0	20
4	18, 26, 29, 37	4	7 of 7	NR	NR	NR	2	1	6
1	26	1	NR	NR	NR	NR	NR	NR	21
1	8	1	NR	c.601G>C	0	1	NR	NR	22
1	4	1	NR	NR	NR	NR	NR	NR	23
21	21, 27, 27, 28, 31, 32, 35, 35, 36, 40, 40, 41, 44, 45, 46, 46, 50, 53, 54, 54, 59	21	24 of 24	19 mutation carriers of 19 subjects tested: 10 partial deletions and c.514C>G, c.699C>G, c.430C>T, c.470C>G, c.712G>A, c.553G>C, c.674C>T, c.769G>T, 3-bp insertion at a splice site acceptor site	11	8	15	6	2

(*Continued*)

Table 3 *Continued*

N	Age at ELST diagnosis[a] (yr)	Symptoms at diagnosis (*N*)[b]	No. ears with abnormal audiological examination of ears examined	Germline *VHL* mutation(s)[c]	Mutation consequence[d]		vHL type (*N*)$_e$		Studies
					Truncated protein	Missense mutation	Type 1	Type 2	
3	34, 40, 42	3	2 of 2	NR	NR	NR	1	1	7
1	44	1	NR	NR	NR	NR	1	0	24
1	32	1	NR	C>A transversion at position -1 on the exon 3 splice acceptor	1	0	0	1	25
1	36	1	NR	NR	NR	NR	NR	NR	8
5	27, 31, 34, 40, 42	4	4 of 5	NR	NR	NR	NR	NR	4
1	31	1	1 of 1	NR	NR	NR	1	0	26
1	NR	1	NR	NR	NR	NR	NR	NR	27
1	19	1	NR	c.C712T	0	1	0	1	45
1	29	1	NR	NR	NR	NR	1	0	28
1	37	NR	NR	NR	NR	NR	NR	NR	29
1	33	1	1 of 1	NR	NR	NR	NR	NR	11
1	44	1	2 of 2	NR	NR	NR	1	0	5
1	20	1	NR	NR	NR	NR	NR	NR	30
35	Mean: 31 (range: 11–63)[f]	NR	34 of 38	NR	NR	NR	NR	NR	39
8	NR	NR	NR	7 mutation carriers of 7 subjects tested: 3 x c.500G>A, c. 509T>A, deletion of exon 1, 2 x deletions of exon 1 and 3	3	2	3	5	38
1	NR	1	NR	NR	NR	NR	NR	NR	31
1	25	1	NR	c.194CtoT	0	1	1	0	32
10	Mean: 39 (range: 28–50)[g]	10	NR	NR	NR	NR	NR	NR	40
2	17, 15[f]	2	NR	NR	NR	NR	NR	NR	33
3	16, 33, 46	2	NR	p.Asp92Gly, p.Leu158Pro, p.Val62GlyfsX66	1	2	3	0	34

(*Continued*)

Table 3 *Continued*

N	Age at ELST diagnosis[a] (yr)	Symptoms at diagnosis (*N*)[b]	No. ears with abnormal audiological examination of ears examined	Germline *VHL* mutation(s)[c]	Mutation consequence[d]		vHL type (*N*)$_e$		Studies
					Truncated protein	Missense mutation	Type 1	Type 2	
1	11	NR	NR	c.217C>T	1	0	1	0	35
1	33	1	NR	553+1G>A	1	0	1	0	36
2	18, 21	2	NR	c.337C>T, c.345C>G	1	1	1	1	37
5	30, 41, 41, 47, 55	3	4 of 5	Deletion of exon2, p.Ser183X, p.Arg161X, p.Ser65Leu, p.Arg167Trp	3	2	5	0	Present study
Total									
140	Median 33 (range: 4–59) $N = 70$	96% (90 of 94)	94% (96 of 102)	51 subjects with reported *VHL* mutations	59% (30 of 51)	41% (21 of 51)	71% (51 of 72)	29% (21 of 72)	

[a]In subjects with bilateral ELST, only the age at the time of the first diagnosed ELST is included. In the calculation of total median age at ELST diagnosis among all subject for whom age at diagnosis was reported, subjects for whom only age at symptom onset or time of resection were reported, are not included (see footnotes *f* and *g*).
[b]Symptoms in the form of hearing loss, tinnitus, vertigo, disequibrillium, aural fullness, aural pain, and/or facial nerve paresis/weakness.
[c]We only included cases in which the specific type of *VHL* mutation was reported.
[d]Consequence of reported mutations was evaluated based on the reference coding nucleotide sequence of the *VHL* NC_000003.11, 624 nucleotides long. In cases where no reference sequences for mutations were given and mutations did not correspond with our applied reference sequence (in italics), most likely mutation consequences were evaluated.
[e]Type 1: If no pheochromocytomas were reported in subject and/or in affected family members, and type 2: If pheochromocytomas were reported in subject and/or in at least one affected family member.
[f]Age at time of symptom onset.
[g]Age at time of resection.
NR, not reported.

(http://icmm.ku.dk/english/icmm-staff/marie_luise_bisgaard/vhl_collaborative_research/).

High-resolution MRI of the inner ear is considered to be the gold standard in ELST diagnosis.[1,4,41,48,49] Nevertheless, many radiologic differential diagnoses exist for ELSTs such as paragangliomas, inner ear adenomas, inflammatory pseudotumors of the endolymphatic sac, and especially for vHL patients: hemangioblastomas and metastases from renal carcinoma.[30,41,50]

Diaz et al.[30] have pointed out that with increasing focus on ELSTs as a part of vHL and simultaneous increased use of high-resolution MRI in inner ear diagnosis, more contrast-enhancing lesions of various origin are likely to be identified near the endolymphatic sac, increasing the rate of false-positive ELST diagnoses. Some lesions are radiologically indistinguishable from ELSTs, and histology is the only sure way of differentiation.[30] In the meta-analysis, histological diagnosis of the ELSTs was only reported for approximately two third of cases. MRI-visible ELSTs that do not cause audiologic abnormalities could represent a margin of error of radiologic diagnosis. The true fraction of radiologically misdiagnosed ELSTs is unknown, as reports of tumors initially misdiagnosed as ELSTs are unlikely to be published. Also, especially small ELST may be overlooked on vHL patients' regular MRI surveillances if inner ear structures are not specifically evaluated. Manski et al.[1] demonstrated that routine MRI of the posterior fossa missed 20% (3/15) of ELSTs that were visible on an MRI that also focused on the petrous bone. In the prospective study, two of the five MRI-diagnosed ELSTs had been missed on two and three previous brain surveillance MRIs before this study, on which the lesions could be identified retrospectively. Also, the long duration of symptoms before diagnosis found in the meta-analysis could partly be explained by these radiologic challenges.

Early identification of ELST may pose a dilemma for clinicians toward timing of surgical management of ELSTs: On one hand, the risk of sudden hearing loss may argue in favor of early surgical excision of tumors.[4,6,8] On the other hand, risk of iatrogenic deafness and nerve damage after misdiagnosis and unwarranted operation could point to initial conservative management, as long as the ELST remains stable clinically and radiologically. Peyre et al.[37] recently described a many-year conservative management of two ELSTs, which demonstrated a stuttering growth pattern and a prolonged stability in tumor size for more than 10 years in one case.

Indication for surgical removal weighs more heavily if the patient's bilateral hearing is threatened due to bilateral ELSTs or unilateral deafness in the opposite ear.[6] In previous reports, the frequency of bilateral ELSTs has been reported to be as high as about 30% (14/43 patients),[6] yielding a great risk of bilateral hearing loss. However, previous estimates are likely to be overestimations due to selection and publication bias, as we found a frequency of 11% (16/140) in the combined meta-analysis and prospective study.

We hypothesized that possible genotype-phenotype correlations could help target ELST surveillance through identification of high-risk vHL patients. In the combined data of the meta-analysis and the prospective study, we did, however, not find evidence to suggest that ELST surveillance can be individualized according to *VHL* genotype (Table 3). The proportion of mutations truncating the p.VHL to missense mutations did not differ significantly between ELST patients (59% and 41%) and the general vHL population (70% and 30%).[3]

As current ELST screening recommendations are based on best assessment and vary greatly between countries, there is a considerable need for international and evidence-based screening guidelines. Current Danish ELST screening guidelines, which correlate with the surveillance guidelines from the American vHL Family Alliance (personal communication), recommend one baseline audiometry in adolescence and MRI of the inner ear only when audiovestibular symptoms are present. However, as use of subjective audiovestibular symptoms is too unspecific a measure for ELST, and as manifest hearing loss is generally irreversible, this current approach is not adequate enough to prevent severe audiovestibular morbidity.

Based on our results, audiometry is a suitable first-line screening tool, and we recommend annual audiometry for vHL patients. This approach is minimally invasive and in many countries more easily accessible than regular MRI scans. An optimal interval for ELST surveillance could not be determined based on present results, and annual examinations are based on our best assessment. Further studies with long-term follow-up are needed to determine the optimal ELST surveillance interval.

Preoperative high-resolution MRI is still necessary to support the diagnosis in cases of audiometric ELST suspicion and to preoperatively map the lesion's location and extent. In countries where routine MRI of the central nervous system is performed every 12–36 months as part of a vHL surveillance program, we recommend that specific images of the petrous bone and endolymphatic sac should be included in these examinations.

Determination of audiological ELST characteristics could further target screening, and we have initiated an international collaborative study of audiological ELST characteristics.

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