

OTOLOGY

Endolymphatic sac tumour in von Hippel-Lindau disease: management strategies

Carcinoma del sacco endolinfatico nella sindrome di von Hippel-Lindau: strategie di trattamento

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SUMMARY

Endolymphatic sac tumour (ELST) is infrequent, as emerges from small series reported in the literature. It is a slow-growing malignancy with local aggressiveness and a low risk of distant metastases. It is often misdiagnosed because of the late onset of symptoms and difficulty in obtaining a biopsy. Its frequency is higher in von Hippel-Lindau (VHL) disease (a genetic systemic syndrome involving multiple tumours), with a prevalence of around 25%. The diagnosis is based on radiology, with specific patterns on contrast-enhanced MRI and typical petrous bone erosion on bone CT scan. Our experience of ELST in the years between 2012-2015 concerns 7 cases, one of which was bilateral, in patients with VHL disease. Four of the 7 patients underwent 5 surgical procedures at our institution. Each case is described in detail, including clinical symptoms, and the intervals between symptom onset, diagnosis and therapy. Postoperative morbidity was low after early surgery on small tumours, whereas extensive surgery for large tumours was associated with loss of cranial nerve function (especially VII, IX, X). The critical sites coinciding with loss of neurological function were the fallopian canal, jugular foramen, petrous apex and intradural extension into the posterior cranial fossa. Early surgery on small ELST is advocated for patients with VHL disease, in whom screening enables a prompt diagnosis and consequently good prognosis.

KEY WORDS: Endolymphatic sac tumour (ELST) • Cerebellopontine angle (CPA) tumour • Temporal bone tumour • Von Hippel-Lindau disease (VHL) • Low-grade adenocarcinoma

RIASSUNTO

Il carcinoma del sacco endolinfatico è un tumore molto raro come evidente dai dati presenti in letteratura ove anche centri di esperienza riferiscono tuttavia casistiche limitate. È un tumore maligno a lenta crescita, con tendenza all'invasione locale e scarsa tendenza alla disseminazione metastatica. L'insorgenza spesso tardiva dei sintomi e la difficoltà ad eseguire indagini biotiche a livello della sede di origine, parete posteriore della rocca, ha reso la diagnosi di questo tumore spesso difficile, nonostante si riconoscano attualmente dati radiologici patognomonic della neoplasia. Pattern tipici di presentazione sono evidenziabili alla RM con mezzo di contrasto e alla TC per osso a strato sottile, rendendo nella maggior parte dei casi possibile la diagnosi radiologica. L'incidenza del tumore del sacco endolinfatico è maggiore nei pazienti affetti da sindrome di von Hippel Lindau (VHL), con una frequenza del 25% che fa parte del quadro sindromico. Negli anni dal 2012 al 2015 abbiamo osservato 7 casi, uno di essi con manifestazione della patologia bilaterale, tutti affetti da VHL. Quattro tra questi sono stati sottoposti a chirurgia presso il nostro centro per un totale di 5 procedure chirurgiche. Ogni caso è stato descritto dettagliatamente analizzando sintomi, intervallo tra comparsa dei sintomi, diagnosi e terapia. Non vi è stata morbidity post-operatoria aggiuntiva nei pazienti in cui la diagnosi e la terapia sono state precoci, mentre la gestione di tumori localmente avanzati è stata associata a deficit neurologici postoperatori, in particolare del VII, IX e X nervo cranico. I siti anatomici critici di coinvolgimento della malattia che hanno coinciso con un pianificato rischio di danno neuronale sono risultati essere il canale di Falloppio, il forame giugulare, l'apice della rocca petrosa. L'estensione intradurale nella fossa cranica posteriore è stato un altro elemento caratterizzante i tumori in stadio avanzato. I tumori del sacco endolinfatico che lo screening permette di evidenziare precocemente nei pazienti VHL, hanno buona prognosi quando affrontati precocemente, compatibilmente con le esigenze terapeutiche della malattia di base.

PAROLE CHIAVE: Tumore del sacco endolinfatico • Tumore dell'angolo ponto-cerebellare • Tumore dell'osso temporale • Sindrome di von Hippel-Lindau • Adenocarcinoma a basso grado

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Introduction

Endolymphatic sac tumour (ELST) is a rare malignancy originating from the endolymphatic system¹⁻⁴. Embryologically, the sac derives from the neuroectoderm and is

located on the posteromedial surface of the temporal bone. ELST was historically classified as primary adenomatous tumour of the temporal bone, and was not clearly defined until the end of the 1980s when Gaffey et al. distinguished

it from adenomatous temporal bone tumours, which have a benign behaviour. The biological pattern and aggressive growth of ELST was found to resemble a papillary histology⁵. Benecke et al. subsequently described middle ear tumours with a papillary growth pattern that were more aggressive and associated with significant bone and dural involvement⁶. With the aid of histological, ultrastructural and immunohistochemical studies, Heffner established in 1989 that papillary tumours of the temporal bone originated from the endolymphatic sac epithelium, and not from the middle ear mucosa as previously believed⁷. Aggressive papillary tumours of the temporal bone were reclassified as ELST by Li et al. in 1993⁸ and the World Health Organization tumour classification has now recognised ELST is synonymous with Heffner tumour and aggressive papillary adenoma. Recent studies have confirmed that these tumours arise specifically from the endolymphatic sac/duct tissue⁹. Sporadic cases are relatively rare^{10,11}, the largest series being accumulated over a period of 30 years¹². ELST is syndromic in von Hippel-Lindau (VHL) disease, with a prevalence of up to 24%⁹. Patients with VHL syndrome are also more likely to have bilateral ELST, seen in up to one in three cases¹¹.

VHL disease is a genetic disorder inherited as an autosomal dominant trait with a variable expression. It is caused by inactivation of the VHL tumour suppressor gene. This mutation predisposes patients to multiple haemangioblastomas of the central nervous system, and tumours and cysts in various organs, such as clear cell renal carcinoma, pheochromocytoma and pancreatic serous cystadenoma¹³⁻¹⁵. A gene responsible for VHL disease has been mapped on the short arm of chromosome 3¹⁰. In sporadic cases, tumorigenesis is associated with somatic alterations of both alleles of the tumour suppressor gene¹⁵. No cases of distant metastases have been reported, whereas local aggressiveness has been well documented.

Late-onset symptoms relating to tumour growth include neurological disability with severe vestibulocochlear and facial cranial nerve impairments. Typical early symptoms caused by ELST are tinnitus (~92%), vertigo and disequilibrium (~62%), and sensorineural hearing loss (~95%). These may be caused by intralabyrinthine haemorrhage or endolymphatic hydrops irrespective of tumour size¹⁶. Its location in the posteromedial wall of the petrous bone allows the tumour to spread posteromedially into the cerebellopontine angle, superiorly into the medial cranial fossa, laterally to the middle ear and anteromedially towards the cavernous and sphenoid sinuses.

Slow growth is the main reason why ELST is classified as a minimally malignant tumour¹⁷ and also explains why it is difficult to diagnose at an early stage. ELST remains relatively asymptomatic until significant surrounding tissue destruction has occurred; the severity of the related functional impairment depends on the sites and subsites affected by tumour extension¹⁰.

A review of the literature showed an increase in the number of cases reported in the last decade, even though the disease remains rare; this could be attributed to improvements in imaging methods and to screening of VHL patients¹⁸. While sporadic tumours are usually diagnosed as a result of symptoms prompting specific petrous bone imaging (contrast-enhanced MRI and bone CT scan), screening in VHL disease enables early detection of the tumour.

When part of the VHL syndrome, the tumour has a relentless and more aggressive growth, and its onset is at a younger age than in sporadic cases¹⁶. When early diagnosis is followed by early surgery, hearing loss is the price to pay in terms of surgical morbidity (though there are some reports in the literature of cases in which hearing was preserved)¹⁹. The origin of the tumour being well-established, if left untreated its growth can involve critical sites such as the fallopian canal, jugular foramen and cerebellopontine angle, and subsequent surgical morbidity is severe²⁰.

Our experience of ELST in VHL in the years between 2012-2015 is described herein, together with a discussion of the main diagnostic and therapeutic controversies of this infrequent disease.

Materials and methods

This was a retrospective analysis on all cases of ELST managed at the Department of Otolaryngology of Padua University Hospital between January 2012 and September 2015.

We reviewed the clinical, audiological, radiological, surgical and pathological records of 7 consecutive ELST patients. Four patients underwent resection with 5 surgical procedures (one patient had a bilateral procedure performed elsewhere, then came to our attention with bilateral residual disease and was treated with further surgery, and is awaiting a cochlear implant). The other 3 cases were not surgically treated and, up to now, managed differently.

This study included only adult patients with a clinical or genetic diagnosis of VHL syndrome. All patients were assessed at the Department for Hereditary Tumours and Oncological Endocrinology of the Istituto Oncologico Veneto. VHL mutations were ascertained from peripheral blood samples using Southern blotting, fluorescence in situ hybridization and complete gene sequencing.

Common clinical manifestations included hearing loss, tinnitus, vertigo, dizziness, aural fullness, balance disturbances, ear pain and facial nerve palsy. Large tumours growing posteromedially caused symptoms secondary to cerebellopontine angle invasion, or lower cranial nerve palsy due to jugular foramen invasion.

Audiological examination was conducted with pure tone audiometry (air and bone conduction thresholds) and vo-

cal audiometry (speech reception thresholds and discrimination loss); the four-frequency pure-tone average based on air conduction thresholds at 0.5, 1, 2 and 4 kHz was used to judge the degree of hearing loss.

Facial nerve function was measured according to the House-Brackman scale, and was tested by electromyography of the cranial district. Subjects were assessed on unenhanced high-resolution computed tomography (CT) scans and contrast-enhanced high-resolution magnetic resonance imaging (MRI) of the temporal bone; diagnostic magnetic resonance sequences analysed were T1-weighted (with and without contrast), T2-weighted, and fluid attenuated inversion recovery (FLAIR) (with and without contrast).

Radiological findings typically included: retrolabyrinthine involvement with focal erosion of the posterior wall of the petrous bone, intratumoural calcification with calcified spicules on CT scan, hyperintense focal signals on T1-weighted (unenhanced) MRI and heterogeneous signals on T2-weighted MRI.

Surgical specimens of resected tumours were routinely stained with haematoxylin and eosin for immunohistochemical analysis.

Surgery was performed by the same team of ENT surgeons. During the follow-up, patients underwent clinical/audiological examination every 6 months and MRI annually. All patients gave their verbal consent to participation in the study.

Results

Our series consisted of 7 patients, 5 females and 2 males, aged 35–62 years (mean 42.7). Table I lists the clinical and

audiological examinations carried out on all patients, and Table II the surgical and postoperative details for patients who underwent skull-base surgery. Four of the 7 patients underwent surgery with radical intent, while 3 have yet to be treated surgically. The 3 cases who were not yet operated on, are detailed herein. In VHL syndrome, the presence of concomitant cerebral, cerebellar or brainstem tumours with impending risk or neurologic sequelae involved the necessity to postpone surgical treatment of ELST in favour of other more urgent conditions.

One 36-year-old woman (patient 6) had a bilateral neurosurgical procedure elsewhere and presented with bilateral residual disease involving the petrous bone and bilateral deafness. Transpetrous revision surgery and cochlear implant was scheduled at our institution, but at the time of writing the latter had been postponed due to the concomitant need to operate on a cerebellar haemangioblastoma.

One patient who was totally deaf on the affected side (patient 5) had undergone surgery via a neurosurgical approach 10 years earlier, at the age of 30, followed by postoperative radiotherapy (60 Gy multifractionated), and had residual disease in the petrous bone, which had since been growing. A period of at least 10 years was judged necessary before any new surgical treatment could be performed on an irradiated petrous bone to prevent infectious sequelae, such as osteonecrosis or osteomyelitis. The patient will be a candidate for revision surgery with trans-labyrinthine approach after 10 years have elapsed.

Patient 7 presented with a tumour involving the petrous bone, the jugular foramen area and the cerebellopontine angle, having recently been treated for a cerebellar haemangioblastoma on the same side, via a neurosurgical approach. ELST was not properly identified at radiology,

Table I. Clinical and audiological examinations in ELST patients.

Patient	Age (years)	Gender	Side	Audiometry	FN impairment	HB	Other symptoms	Other VHL manifestations
1 – C.G.	62	F	L	Moderate SN hearing loss	No	I	Ear pain	CNS Hbs, ret. Hbs, RCC, renal cysts, pancreatic cysts
2 – C.A.	35	F	R	Total deafness	No	I	None	CNS Hbs, ret. Hbs, renal cysts, pancreatic cysts
3 – M.S.	42	F	R	Severe SN hearing loss	Moderate neuropathy at EMG	I	Vertigo, tinnitus	Ret. Hbs, renal cysts, Pheo, pancreatic cysts
4 – M.P.	38	F	R	Severe SN hearing loss	Severe neuropathy at EMG	I	Tinnitus, imbalance, facial paresthesias	CNS Hbs, Pheo
5 – C.I.R.	36	F	L	Severe SN hearing loss	No	I	None	CNS Hbs, RCC bilat., renal cysts, pancreatic cysts
6 – C.L.	37	M	Bilateral	Left severe SN hearing loss; right deafness	No	I	None	CNS Hbs, ret. Hbs, RCC, renal cysts, pancreatic cysts
7 – V.F.	49	M	R	Total deafness	No	I	Imbalance	CNS Hbs, ret. Hbs, RCC, renal cysts, pancreatic cysts

Abbreviations: SN, sensorineural; FN, facial nerve; HB, House-Brackmann; Hbs, haemangioblastoma; ret., retinal; RCC, renal clear cell carcinoma; Pheo, pheochromocytoma

Table II. Surgical and postoperative details of treated patients.

Patient	Surgical approach	FN function post-op (HB)	Diagnostic delay (months)	Therapeutic delay (months)	Follow-up (months)
1 – C.G.	Translabyrinthine	I	41	5	50
2 – C.A.	(Retrosigmoid - 11 years before) Translabyrinthine	I	(36) 2	(12) 7	43
3 – M.S.	Translabyrinthine	I	64	20	37
4 – M.P.	1^: Petrooccipital transsigmoid + translabyrinthine 2^: Subtotal petrosectomy	1^: III 2^: V	24	100	36

and was initially considered an extension of the haemangioblastoma, but intraoperative findings confirmed the diagnostic suspicion of concomitant, aggressive ELST originating from the petrous bone. The patient experienced postoperative IX to XII nerve palsy, which was given time to compensate before planning another procedure on the jugular foramen that would involve a definitive paralysis of the nerves.

On retrospective review of our ELST patients, delays emerged between symptom onset and diagnosis, and between diagnosis and treatment. The mean delay between diagnosis and surgery was 33 months (range: 5 months to 8 years).

In patients 1 (Fig. 1) and 2, the sites of tumour involvement were the endolymphatic sac, labyrinth and dura of the posterior fossa; in patients 3 and 4 (Fig. 2), who had the greatest diagnostic and therapeutic delays, the tumour extended to and infiltrated the jugular bulb and infra-labyrinthine area.

No perioperative or postoperative complications were recorded. Postoperatively, the facial nerve was intact in 3 of the 4 surgically-treated cases; the fourth (patient 4) received a graft after intraoperative sacrifice of the facial nerve due to tumour infiltration. All surgical patients are alive and disease-free at mean follow-up of 41.5 months (range 36-50). No adjuvant therapy was administered.

Discussion

ELST is a locally aggressive tumour originating in the endolymphatic sac on the posterior border of the petrous ridge. Its slow but relentless growth into the petrous bone and then into the cerebellopontine angle and middle cranial fossa can involve the surrounding neurovascular structures, such as the carotid artery and the cranial nerves from VII to XII. The VI cranial nerve involves the tumour's extension into the petrous apex, which is infrequent but possible²¹.

Before being reclassified, ELST was underestimated and for years it was often misinterpreted as paraganglioma, metastatic renal cell carcinoma, choroid plexus papilloma, ceruminous gland adenocarcinoma, or aggressive papillary tumour⁸. Its diagnosis is radiological, and it has quite a specific pattern of presentation: a retrolabyrinthine

location with focal erosion of the posterior wall of the petrous bone, intratumoural calcification with calcified spicules on CT scan, hyperintense focal signals on T1-weighted (unenhanced) MRI scan, markedly heterogeneous enhancement after gadolinium and heterogeneous signal on T2-weighted sequences²²⁻²⁴.

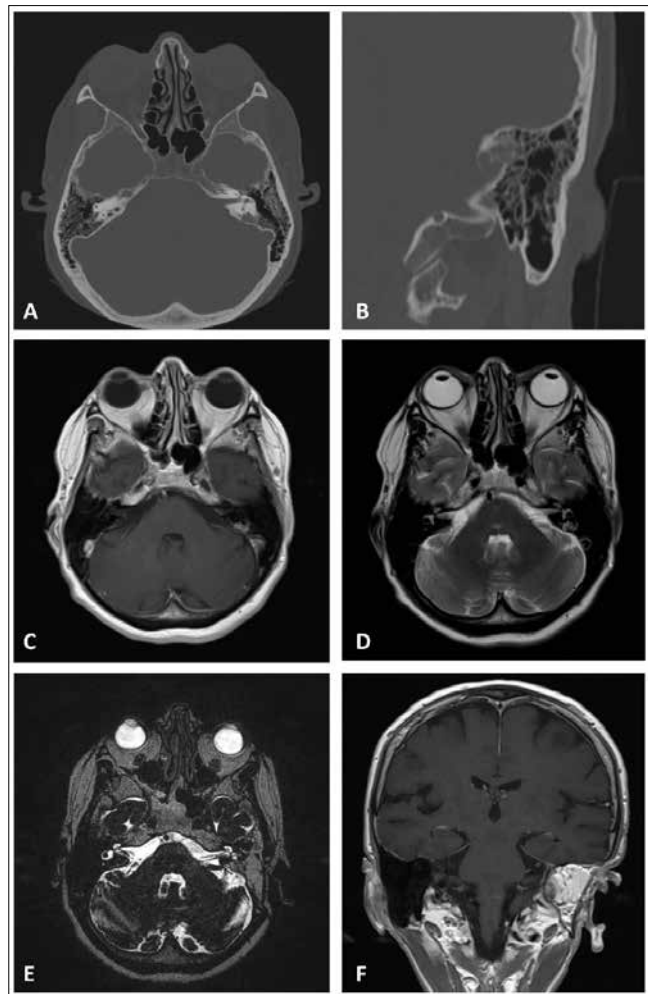


Fig. 1. Small left endolymphatic tumour. A: axial bone CT scan with erosion in posterior ridge of petrous bone. B: bone erosion and tumour seen in retrolabyrinthine area in a coronal plane. C: axial contrast-enhanced T1 MRI showing tumour in petrous bone, in the prestigmoid-extradural area. D: axial T2 MRI showing hyperintense signal in tumour foci. E, F: no residual disease evident on T2 high-resolution and contrast-enhanced T1 MRI.

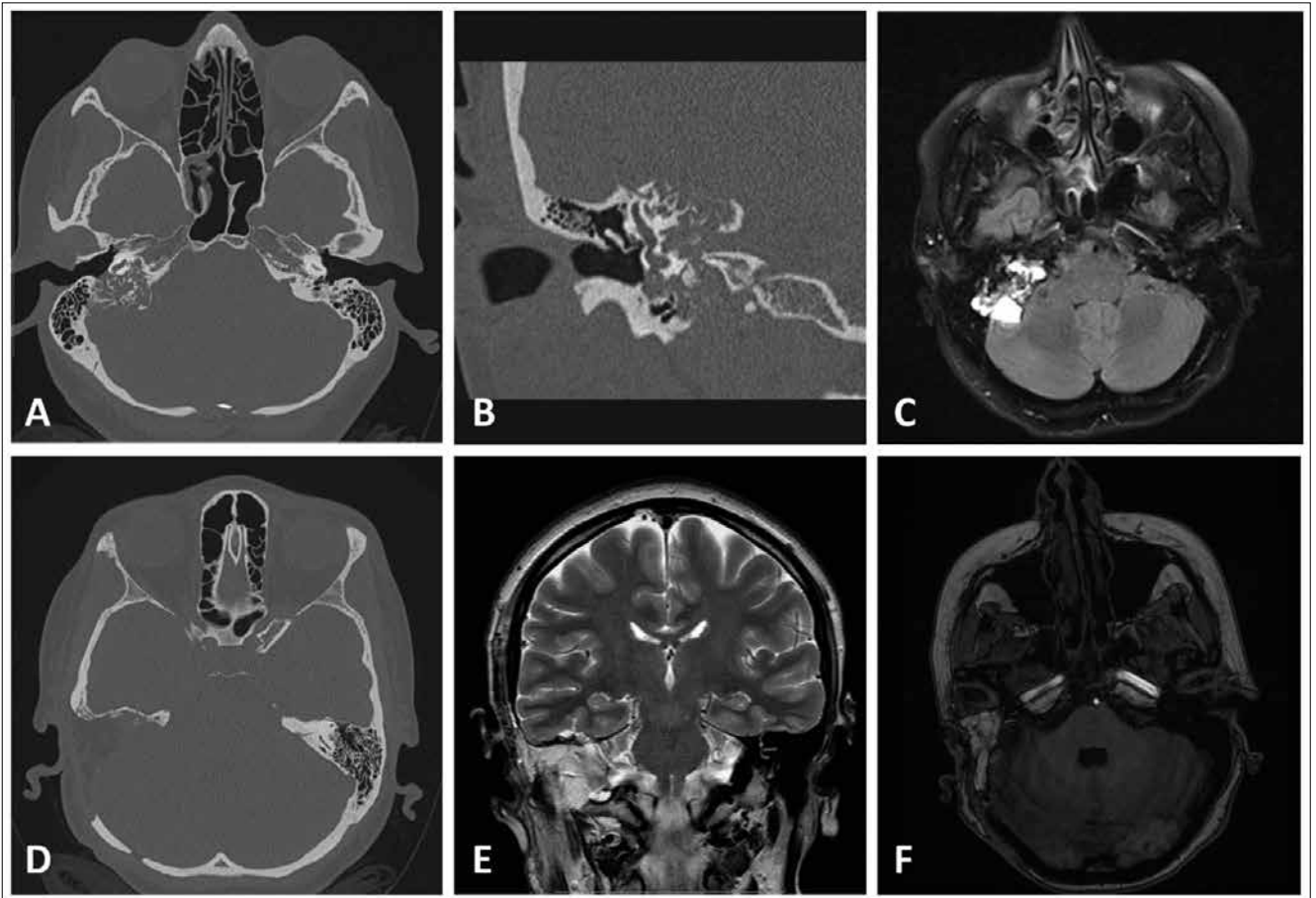


Fig. 2. Extended right endolymphatic tumour. A: axial bone CT scan with extended erosion in petrous bone. B: bone erosion and tumour seen in retrolabyrinthine area in a coronal plane. C: axial T2 MRI with flair, showing tumour in the petrous bone and posterior cranial fossa. D: axial bone CT scan after the first surgical step, showing the area of drilled bone of a lateral petrosectomy and the retrosigmoid craniotomy. E: coronal T2 MRI after the first surgical step. F: no residual disease visible on contrast-enhanced T1 MRI after the second surgical step.

It is easier to diagnose in small lesions, when the tumour's origin is still pathognomonic. On the other hand, when the disease involves the jugular foramen or the intradural compartment, extensive bony destruction prevents the typical origin of the tumour from being established^{25,26}.

Further investigations might be useful to rule out intracranial vessel involvement in order to plan safe surgery. Arteriography may give information about carotid artery infiltration, or when part of the approach or in case of disruption or planned sacrifice: in such cases, a balloon occlusion test may be added. In our series, it was never necessary.

It is essential to consider the differential diagnosis, although in VHL patients ELTS may be a presenting sign of the syndrome.

Treatment of ELTS demands extensive surgery with adequate bone removal around the area of macroscopically evident tumour. Lateral skull base approaches each have their intrinsic morbidity²⁷ but, in principle, morbidity is directly proportional to the extension of the tumour. Microsurgical approaches through the temporal bone are directed to the site of origin of ELST along the petrous ridge

and the surrounding subsites of tumour involvement, and may be combined if required.

A transmastoid-retrolabyrinthine approach is for a small endolymphatic tumour, with no extension in the surrounding subsites. The translabyrinthine approach is for larger tumours, with poor hearing and extending through the labyrinth and/or intradurally in the posterior fossa. The involvement of the middle ear is better managed through a petrosectomy, lateral or subtotal²⁷. When ELST extends to the jugular foramen, POTS²⁸ allows good and safe exposure of the infralabyrinthine and jugular foramen area. Similarly, involvement of the petrous apex or the middle cranial fossa, is managed by combining a transmastoid-transpetrous approach with a subtemporal/middle cranial fossa approach. The pure retrosigmoid approach, directed to the intradural extension of the tumour in the posterior fossa, may be not large enough to allow extensive drilling of the petrous bone around the site of origin of ELST.

Small tumours, as seen when ELTS is diagnosed early and treated promptly, entail hearing loss but no further morbidity. When hearing is already impaired, there can be no doubt about the advisability of surgery for early le-

sions. When hearing is unaffected (an infrequent situation that may be encountered on screening or in the case of incidentally-found tumours), it is nonetheless at risk. As a rule, it is difficult to ensure the removal of even a very small tumour within the endolymphatic sac and vestibular aqueduct without hearing loss or impairment, although some experiences of hearing preservation after the resection of very small tumours have been described^{12 19 29}. Hearing preservation after early surgery for very small tumours seems a distinctly sporadic event, and should not (in our opinion) be presented as a likely outcome when proposing surgery to patients. Any disruption of the endolymphatic sac and vestibular aqueduct can be a cause of hearing loss, per se, even in patients with very small tumours.

If the tumour is left untreated and reaches surrounding subsites like the fallopian canal with the facial nerve, jugular foramen area, petrous apex and intradural compartment of the cerebello-pontine angle and middle cranial fossa, the related surgical morbidity is a completely different story. Bambakidis²¹ proposed a classification of ELST based on size and sites of extension, but does not reflect the problems of the related surgical morbidity, since this is already evident for stage I tumours.

Early diagnosis and prompt therapy are key to avoid unavoidable foreseeable tumour extension into critical sites. When aggressive and extensive surgery is required, the prognosis is unfavourably affected because of the related surgical morbidity, and radicality is rarely achievable even with very extensive surgery.

The effectiveness of radiotherapy (stereotactic or fractionated) is still unclear, without any evident benefit in long-term prognosis for patients¹⁰. Postoperative radiotherapy in subtotal resection may give some beneficial results, but with a risk of relapse > 50%⁹.

Since ELST can be a facet of VHL disease, accurate screening should be considered to detect the tumour early and thus offer patients early surgery with a good prognosis, good long-term disease-free survival rates and limited treatment-related morbidity³⁰. Delaying treatment is not uncommon in patients with the syndromic form of ELST, due to the complexity of VHL disease, with multiple tumour localisations in other body districts that often require prompt surgery¹⁶. In principle, awareness that early surgery for small tumours is associated with a low impact in terms of morbidity and a prompt recovery after the procedure should enable the treatment of ELTS to be scheduled appropriately in the frame of VHL.

Clinical-radiological screening in VHL populations at risk of ELST may favourably affect prognosis, providing that early diagnosis is followed by prompt therapy.

When the tumour is bilateral – a situation seen in 30% of syndromic patients³ and, to the best of our knowledge, never reported in sporadic cases – there is the problem of bilateral deafness as the natural outcome of the evolution

of the disease. The mechanisms behind it are direct invasion of the inner ear, endolymphatic hydrops that mimic Meniere's disease³¹, and intralabyrinthine haemorrhage (even in small tumours), which is responsible for sudden sensorineural hearing loss³².

Early rehabilitation with a cochlear implant may be the solution, but the tumour has to be resected before it reaches and destroys the cochlea as well as the posterior labyrinth. Though not involved directly, damage to the posterior labyrinth (vestibule or/and semicircular canals) and surgical trauma associated with tumour removal may cause ossification in the cochlea and prevent its proper functioning, or even the insertion of the cochlear implant³³.

There seem to be sporadic cases of hearing preservation after early surgery for very small tumours, but it would be wrong (in our opinion) to consider sparing natural hearing as one of the goals of any proactive surgery. Disruption of the endolymphatic sac and vestibular aqueduct suffices in itself to cause hearing loss, even in patients with very small tumours.

Conclusions

ELTS is infrequent and usually misdiagnosed, but screening for this cancer can be routinely performed in VHL patients. The most appropriate timing of its treatment should be established for the purpose of achieving a low morbidity by performing early surgery on a small tumour.

Hearing is always at risk when surgery is performed for ELST, but preserved normal hearing in a patient with detectable ELST is unusual; hearing loss is generally identified already at diagnosis, even in the case of small tumours. There have been some sporadic reports of hearing being preserved after surgery for ELTS^{19 29}.

A 'wait-and-see' strategy can only be a temporary solution for ELTS in VHL disease to enable the treatment of multiple tumours to be planned. The slow, but relentless growth of ELTS – especially in syndromic cases – leads to unfavourable outcomes once critical structures have been affected, because they cannot be spared, meaning that postoperative morbidity is significant and long-term disease control rates are low.

Screening VHL patients for the early detection of ELST is very important in order to ensure the most favourable timing of radical surgery and the least possible morbidity.

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