

## Seminar

## von Hippel-Lindau disease

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**von Hippel-Lindau disease is a heritable multisystem cancer syndrome that is associated with a germline mutation of the *VHL* tumour suppressor gene on the short arm of chromosome 3. This disorder is not rare (about one in 36 000 livebirths) and is inherited as a highly penetrant autosomal dominant trait (ie, with a high individual risk of disease). Affected individuals are at risk of developing various benign and malignant tumours of the central nervous system, kidneys, adrenal glands, pancreas, and reproductive adnexal organs. Because of the complexities associated with management of the various types of tumours in this disease, treatment is multidisciplinary. We present an overview of the clinical aspects, management, and treatment options for von Hippel-Lindau disease.**

von Hippel-Lindau disease is an autosomal dominant neoplasia syndrome that results from a germline mutation in the *VHL* gene.<sup>1-6</sup> Germline mutations in the *VHL* gene lead to the development of several benign or malignant tumours, and cysts in many organ systems. Affected individuals might develop CNS lesions including cerebellar, spinal cord, brainstem, nerve root, and supratentorial haemangioblastomas, as well as retinal haemangioblastomas and endolymphatic sac tumours (table 1)<sup>5,7-17</sup> (figure 1). Visceral features of the disorder include renal cysts and carcinomas, pheochromocytomas, pancreatic cysts and neuroendocrine tumours, as well as epididymal and broad ligament cystadenomas (table 1, figure 1).

von Hippel-Lindau is not rare (incidence is roughly one in 36 000 livebirths),<sup>18,19</sup> and has over 90% penetrance by 65 years of age.<sup>20</sup> Before comprehensive screening surveys became routine, median survival of patients with the disease was less than 50 years of age. The main causes of death were complications linked to renal cell carcinomas and CNS haemangioblastomas.<sup>7-9,20,21</sup> Improved surveillance, earlier diagnosis of lesions by modern imaging and laboratory studies (panel 1), improvements in treatment, and increased knowledge of this disease have improved prognosis and reduced the complications related to these tumours.

Because of the progressive, diverse nature, and high frequency of multiple neoplasms in various organ systems, the management of the tumour types is complicated by the presence of others. A multispecialty team is needed for the optimum assessment and treatment of these patients. Comprehensive serial screening and routine scheduled follow-up are essential for proper care (panel 1).<sup>22</sup> We review the molecular events underlying tumour formation in von Hippel-

	Mean (range) age of onset (years)	Frequency in patients (%)
<b>CNS</b>		
Retinal haemangioblastomas	25 (1-67)	25-60%
Endolymphatic sac tumours	22 (12-50)	10%
Craniospinal haemangioblastomas		
Cerebellum	33 (9-78)	44-72%
Brainstem	32 (12-46)	10-25%
Spinal cord	33 (12-66)	13-50%
Lumbosacral nerve roots	Unknown (..)	<1%
Supratentorial	Unknown (..)	<1%
<b>Visceral</b>		
Renal cell carcinoma or cysts	39 (16-67)	25-60%
Pheochromocytomas	30 (5-58)	10-20%
Pancreatic tumour or cyst	36 (5-70)	35-70%
Epididymal cystadenoma	Unknown (..)	25-60%
Broad ligament cystadenoma	Unknown (16-46)	Unknown

See references 5,7-17.

Table 1: Frequency of lesions and age at onset of von Hippel-Lindau disease lesions

Lindau disease, discuss the salient clinical, laboratory, pathological, and radiographical findings, and examine current treatment options for lesions associated with the disease.

### Molecular genetics

*VHL* is a tumour suppressor gene on the short arm of chromosome 3 (3p25-26).<sup>23</sup> Most people with the disorder inherit a germline mutation of the gene from the affected parent, and a normal (wild type) gene from the unaffected parent. According to Knudson's two-hit hypothesis of tumorigenesis, initiation of tumour formation arises when both *VHL* alleles are inactivated.<sup>24,25</sup> Germline mutations of *VHL* are present in all the cells of affected individuals who inherit the genetic trait. However, only those cells that (1) undergo a deletion or mutation of the remaining wild type allele, and (2) are constituents of susceptible target organs

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### Search strategy

We searched PubMed database using the keyword von Hippel-Lindau, combined with the terms central nervous system, haemangioblastoma, pancreatic neuroendocrine tumour, pheochromocytoma, renal cell carcinoma, or treatment. We focused mainly on manuscripts published during the past 10 years, but have also referenced papers from before that time. Relevant articles that were not identified by this search were also referenced.

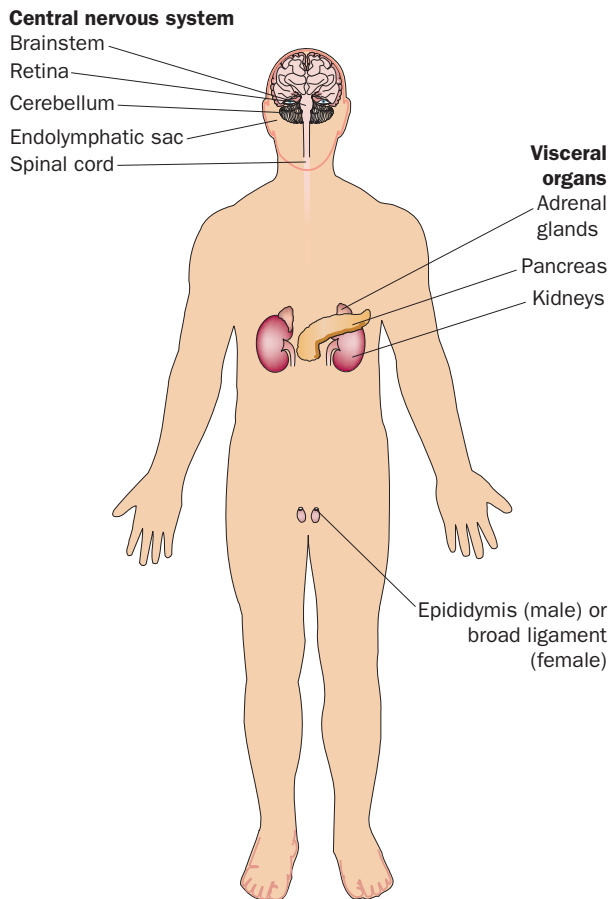


Figure 1: **Affected organs**

(CNS, kidneys, adrenal glands, pancreas, and reproductive adnexal organs) develop tumours. Some investigators have shown somatic inactivation of the *VHL* gene in sporadically occurring CNS haemangioblastomas,<sup>26–29</sup> and renal cell carcinomas.<sup>30–33</sup>

The *VHL* gene has three exons that encode the VHL protein.<sup>23</sup> VHL is a tumour suppressor protein that is localised in the nucleus or cytoplasm, the extent to which being dependent on cell density.<sup>34,35</sup> The protein forms a complex with other proteins including elongin B, elongin C, and Cullin 2 (CUL2), to form the VCB-CUL2 complex (figure 2).<sup>36,37</sup> This protein complex determines ubiquitin-dependent proteolysis of large cellular proteins. When normal oxygen levels are present, the VCB-CUL2 complex binds to, and targets, the  $\alpha$  subunits of hypoxia-inducible factors (HIF) 1 and 2 for ubiquitin-mediated degradation of protein (figure 2).<sup>38</sup>

Abnormal or absent VHL protein function (as in von Hippel-Lindau syndrome) might disrupt tumour-suppression indirectly through HIF-mediated effects (figure 2) or directly through VHL-mediated effects, or both. Many of the tumour suppressive effects of the protein could result from the degradation of HIF. In normal circumstances, HIF can coordinate the cell's response to hypoxia. Through transcriptional regulation, HIF enhances glucose uptake and increases expression of angiogenic, growth, and mitogenic factors including vascular endothelial growth factor (VEGF), platelet derived growth factor  $\beta$  polypeptide (PDGF $\beta$ ), erythropoietin (which can cause polycythaemia that occasionally arises in von Hippel-Lindau), and transforming growth factor  $\alpha$  (TGF $\alpha$ ) (figure 2).<sup>6,39–41</sup>

Subsequently, disruption of VHL-protein-mediated degradation of HIF could contribute to tumour formation through multiple mechanisms (figure 2). If VHL function were absent or abnormal, HIF could stimulate angiogenesis, which is critical for persistence of tumours associated with the disorder. HIF-mediated angiogenesis could result from increased levels of VEGF or PDGF $\beta$ , or both, which are known to be important for proliferation of endothelial cells and pericytes, respectively (figure 2).

This link might explain the highly vascular nature of tumours associated with von Hippel-Lindau disease, especially haemangioblastomas and renal cell carcinomas. Moreover, high vascular permeability of the tumour vessels, resulting from increased VEGF levels, might also underlie the peritumoural oedema and cysts generally present in this disorder.<sup>10</sup> Another potential mechanism of HIF-mediated carcinogenesis is overproduction of TGF $\alpha$ . Besides being a potent mitogenic factor (especially for renal epithelium), raised TGF $\alpha$  can stimulate cellular overexpression of epidermal growth factor receptors (receptors for TGF $\alpha$ ), creating an autocrine loop.<sup>6,40,42–46</sup>

Other possible mechanisms of tumorigenesis caused by absent or abnormal VHL protein, independent of HIF, include disruption of normal cell cycle, increased angiogenesis, and abnormalities in the extracellular matrix. The inability to leave the cell cycle (ie, to enter G<sub>0</sub>) is seen in cells without VHL protein.<sup>43</sup> This event might take place early in tumorigenesis. Furthermore, mutations of the protein itself could increase VEGF expression through incorrect transcriptional and post-translational regulation.<sup>47,48</sup> These mutations might augment the angiogenic effects mediated by HIF and further increase tumour vessel permeability. Finally, although cells without VHL protein can secrete fibronectin, they cannot properly assemble a fibronectin extracellular matrix, which could contribute to carcinogenesis.<sup>42</sup> Overall, HIF-mediated, direct VHL-protein-mediated, and unknown effects of abnormal or absent VHL protein probably interact to induce formation of the various tumours in this disease.

### Clinical diagnosis

Diagnosis of von Hippel-Lindau disease is often based on clinical criteria. Patients with a family history, and a CNS haemangioblastoma (including retinal haemangioblastomas), phaeochromocytoma, or clear cell renal carcinoma are diagnosed with the disease. Those with no relevant family history must have two or more CNS haemangioblastomas, or one CNS haemangioblastoma and a visceral tumour (with the exception of epididymal and renal cysts, which are frequent in the general population) to meet the diagnostic criteria.<sup>9,49,50</sup>

Specific correlations of genotype and phenotype have emerged in affected families. Several familial phenotypes of von Hippel-Lindau disease are now recognised, providing useful information to screen and counsel affected individuals (panel 2). Type 1 families have a greatly reduced risk of phaeochromocytomas, but can develop all the other tumour types generally associated with the disease. Type 2 families have phaeochromocytomas, but have either a low-risk (type 2A) or high-risk (type 2B) for renal cell carcinomas. Type 2C families have phaeochromocytomas only, with no other neoplastic findings of VHL (panel 2).<sup>6,51–56</sup>

### Genetic testing

Advances in genetic testing for the disease include qualitative and quantitative Southern blotting, which has been added to DNA sequence analysis. This improved

### Panel 1: Recommended intervals for screening in 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

Adapted from reference 22. \*Imaging techniques that are generally recommended before and after contrast infusion.

testing has increased the detection rate of DNA mutations in peripheral blood leucocytes from 75% to nearly 100%.<sup>57</sup> In 1996, there were more than 137 distinct intragenic germline mutations reported in affected families in North America, Europe, and Japan.<sup>51</sup> Mutation types included missense, non-sense, microdeletion, insertion, deletion, and splice site.<sup>51</sup> Known mutations of von Hippel-Lindau disease are now stored online (<http://www.umd.necker.fr/>). Since genetic testing detects mutations in nearly 100% of documented affected families, serial clinical surveillance studies are recommended for family members with mutations.

A diagnostic challenge arises in de novo cases (ie, the first affected member of a family) of von Hippel-Lindau disease. These cases arise in as many as 20% of kindreds.<sup>58</sup> The initial mutation in a de novo case might result in disease mosaicism (ie, some, but not all, tissues carry the new disease mutation). Thus, such patients might have clinical signs of the disease, but test negative genetically, because the *VHL* mutation is not carried in all peripheral leucocytes. The earlier the new mutation arises in embryogenesis, the more numerous and varied the types of cells that will carry the mutation. Mosaicism can occur as a mutated gene in somatic tissue only, in germ tissue only, or in both. The risks to a carrier of a new mutation and to their offspring are very different in these three circumstances.

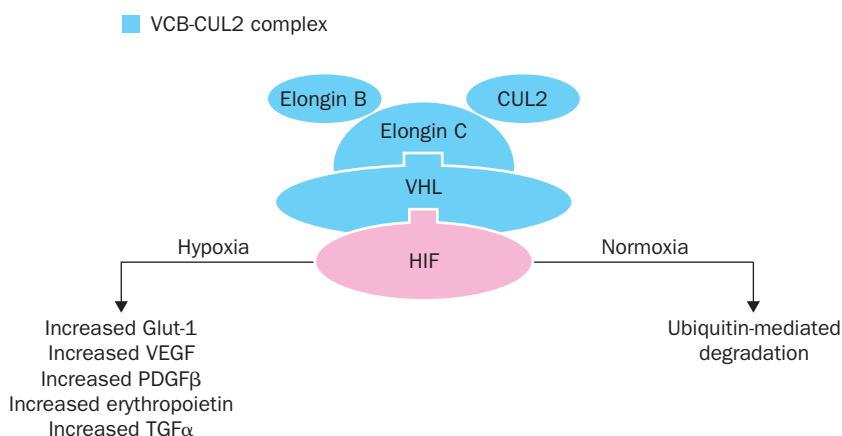


Figure 2: Interaction of VHL protein with other proteins including elongin B, elongin C, and CUL2, to form the VCB-CUL2 complex

Glut-1=glucose transporter 1.

### Central nervous system lesions CNS haemangioblastomas (excluding retina)

#### General features

Haemangioblastomas of the CNS are the most common tumour in von Hippel-Lindau disease, affecting 60–80% of all patients.<sup>11,21,59</sup> The average age of presentation for CNS haemangioblastomas is 33 years (table 1).<sup>11</sup> These tumours are benign, but are a major cause of morbidity. They arise anywhere along the craniospinal axis and are often associated with oedema or cysts (associated cysts occur with 30–80% of haemangioblastomas), or both. CNS haemangioblastomas are generally seen in the spinal cord and cerebellum, followed by the brainstem, lumbosacral nerve roots, and supratentorial region (table 2).

#### Clinical, imaging, and histological findings

Symptoms related to haemangioblastomas depend on tumour location and size, and the presence of associated oedema or cysts.<sup>11</sup> We reviewed the natural history of CNS haemangioblastomas (665 in 160 consecutive patients) as defined by serial MRI.<sup>11</sup> As expected, the tumour volume needed to produce symptoms indicated the spatial capacity wherever the tumour is developing. Smaller lesions in the spinal cord and brainstem were needed to produce symptoms than in the cerebellum. Symptomatic tumours grew ten times faster than asymptomatic tumours; whereas cysts grew 3.2-fold and 1.7-fold faster (symptomatic *vs* asymptomatic) than the haemangioblastoma associated with them. These tumours often have several periods of tumour growth separated by periods of arrested growth; many untreated tumours remain the same size for years. Table 2 shows the most common signs and symptoms associated with haemangioblastomas in various regions of the CNS.

Haemangioblastomas of the craniospinal axis are best assessed by contrast-enhanced T1-weighted MRI (panel 1). These tumours can be easily identified and quantified by radiography. T2-weighted or FLAIR (fluid-attenuated inversion recovery) MRI is used to quantify peritumoural oedema and cysts (panel 1). Arteriography typically shows intense persistent staining of the haemangioblastoma, arteriovenous shunting, and early draining veins.

Haemangioblastomas are well defined, thinly encapsulated tumours that appear bright red at operation. Histologically, they consist of a rich vascular plexus that is surrounded by polygonal stromal cells (figure 3). The stromal cell is neoplastic in origin.<sup>60,61</sup>

#### Treatment

Most haemangioblastomas of the craniospinal axis can be safely and completely excised by surgery.<sup>10,12,62</sup> Haemangioblastomas in the CNS often grow at several sites simultaneously, new lesions can arise with time, and the growth pattern of these tumours can be irregular and unpredictable, therefore resection is deferred until the onset of symptoms to avoid unnecessary surgery.<sup>10–12</sup>

Preoperative embolisation is done at some centres to reduce tumour vascularity before resection. Generally, we do not use embolisation, since these tumours can be excised with minimum blood loss if the basic tenets of circumferential microsurgical excision are followed.<sup>10,12,62</sup>

### Panel 2: Genotype-phenotype classifications in families with von Hippel-Lindau disease\*

	Clinical characteristics
Type 1	Retinal haemangioblastomas CNS haemangioblastomas Renal cell carcinoma Pancreatic neoplasms and cysts
Type 2A	Phaeochromocytomas Retinal haemangioblastomas CNS haemangioblastomas
Type 2B	Phaeochromocytomas Retinal haemangioblastomas CNS haemangioblastomas Renal cell carcinomas Pancreatic neoplasms and cysts
Type 2C	Phaeochromocytoma only

\*Endolymphatic sac tumours and cystadenomas of the epididymis and broad ligament have not been assigned to specific von Hippel-Lindau types.

Because of the potential morbidity associated with resection of multiple craniospinal haemangioblastomas in von Hippel-Lindau disease, stereotactic radiation therapy has been used instead.<sup>63-68</sup> Small haemangioblastomas (<3 cm diameter), and those not associated with cysts might respond safely to radiation therapy.<sup>63-68</sup> However, studies with longer assessment and more patients than those done so far, are needed to establish effectiveness and potential long-term effects of this treatment.

#### Retinal hemangioblastomas

##### General features

Retinal haemangioblastomas (retinal angiomas) are one of the most common tumours in von Hippel-Lindau disease, and are seen in as many as 60% of patients (table 1).<sup>13,14,50</sup> They arise in the periphery, or on or near the optic disc, or both. They are often multifocal and bilateral (about 50%). The mean age of patients at presentation is 25 years, but 5% of retinal angiomas present in patients younger than 10 years of age.

##### Clinical, imaging, and histological findings

Retinal angiomas are symptomless in the initial stages, and are detectable only by examination of the dilated eye. Despite being asymptomatic, they can lead to part or total loss of vision. Peripheral tumours cause visual symptoms through their growth, increased vascular permeability (which leads to accumulation of subretinal fluid), and the development of hard exudates at the macula. Tumours on the optic disc behave similarly. Both peripheral and central angiomas can cause exudative and tractional retinal detachment as they enlarge.

Ophthalmoscopy with pharmacological dilation of the iris allows identification of most retinal tumours (figure 4). Fluorescein angiography is used to assess macular function associated with peripheral and optic nerve lesions. Screening examinations with dilated funduscopy should be done at least once a year starting at age 1 year (panel 1). Ophthalmologists specialising in vitreoretinal disease should provide the ophthalmological management of patients with von Hippel-Lindau disease.

Retinal haemangioblastomas are grossly and histologically identical to craniospinal haemangioblastomas.<sup>69</sup>

##### Treatment

Early diagnosis and treatment can prevent visual loss or blindness. Most peripheral retinal tumours respond to laser photocoagulation or cryotherapy.<sup>70</sup> Vitrectomy should be considered for patients with substantial tractional detach-

	Frequency of haemangioblastomas in nervous system*	Signs and symptoms (%)*
Cerebellum	37%	Gait ataxia (64%), dysmetria (64%), headaches (12%), diplopia (8%), vertigo (8%), emesis (8%)
Brainstem	10%	Hypaesthesia (55%), gait ataxia (22%), dysphagia (22%), hyper-reflexia (22%), headaches (11%), dysmetria (11%)
Spinal cord	50%	Hypaesthesia (83%), weakness (65%), gait ataxia (65%), hyper-reflexia (52%), pain (17%), incontinence (14%)

\*Frequency of signs and symptoms of patients who were undergoing resection. See reference 11.

Table 2: Signs and symptoms associated with haemangioblastomas

ment of the retina with a large fibrovascular component. Because of the damage that some treatments including laser photocoagulation can cause, tumours on the optic disc should be monitored without treatment. Enucleation might be necessary for irreversible glaucoma in which severe pain is associated with end-stage ocular angiomatosis.

Various radiotherapy treatments have been applied to cases of severely affected retinas that did not respond to usual methods, but the usefulness of these approaches and their role in management of retinal haemangioblastomas needs to be defined. Anti-VEGF treatment has been reported to restore visual function in a patient with a tumour in the optic nerve head.<sup>71</sup> This experimental approach might provide hope for patients with haemangioblastomas that are not amenable to current treatments.

#### Endolymphatic sac tumours

##### General features

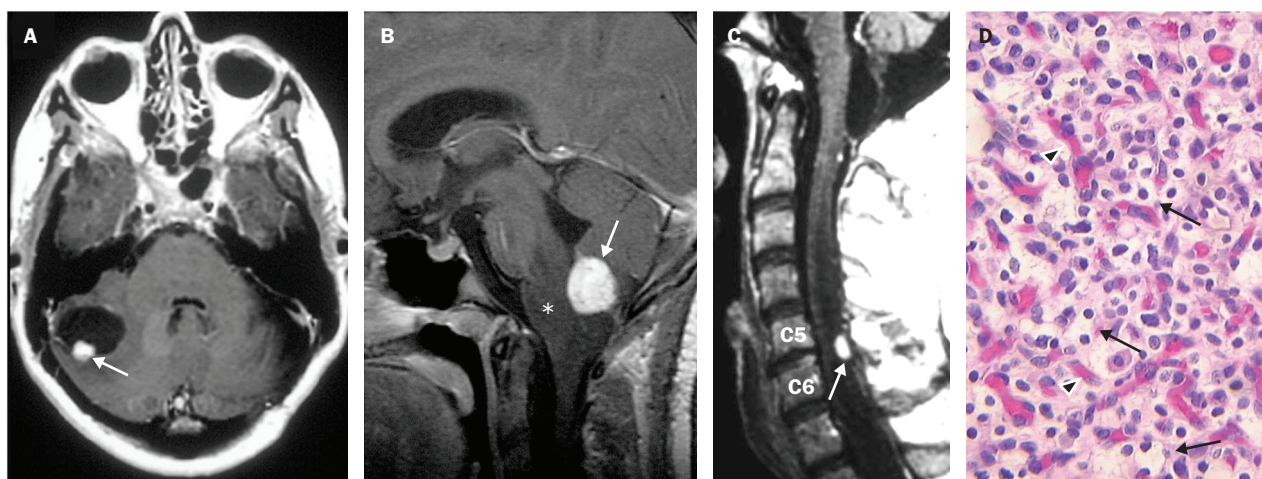
These tumours are rare in the general population, but are frequently associated with von Hippel-Lindau disease.<sup>72</sup> MRI revealed evidence of these tumours in 11% of patients (15 tumours in 13 of 121 patients assessed; the mean age of presentation was 22 years) (table 1). von Hippel-Lindau is the only condition associated with bilateral endolymphatic sac tumours.

##### Clinical, imaging, and histological findings

Patients in whom there is evidence of these tumours from imaging present with part or complete hearing loss (100%), tinnitus (77%), a sense of dysequilibrium (62%), and facial paresis (8%).<sup>72</sup> The frequency of microscopic tumours might be higher than that estimated by imaging, because patients often have vestibulocochlear symptoms with no CT or MRI evidence of such a tumour.<sup>72</sup>

Radiological examination and diagnosis of endolymphatic sac tumours include precontrast and post-contrast CT and MRI of the internal auditory canals (figure 5). In CT images, the tumours are generally isointense with brain parenchyma, but can have focal areas of low and high attenuation. CT of the temporal bones with large tumours shows a destructive or expansive lesion centred in the endolymphatic duct (in between the sigmoid sinus and internal auditory canal). MRI shows either homogeneous or heterogeneous intensity after precontrast T1-weighted imaging. Postcontrast T1-weighted MRI can also show homogeneous or variable patterns of patchy enhancement. Audiograms are used to supplement radiographical data, and to document the presence or progression of hearing loss (panel 1).

Endolymphatic sac tumours are highly vascular, and often erode or expand the surrounding temporal bone.



**Figure 3: MRI and histological features of CNS haemangioblastomas**

(A) Axial T1-weighted contrast-enhanced MRI of a cerebellar haemangioblastoma (arrow) with an associated cyst (homogeneous associated dark region) in a 40-year-old woman. (B) Mid-sagittal T1-weighted postcontrast MRI of medullary haemangioblastoma (arrow) with associated brainstem oedema (asterisk) in a 12-year-old girl. (C) Mid-sagittal postcontrast T1-weighted MRI of the spinal cord of a 50-year-old man. The haemangioblastoma is located in the posterior portion of the spinal cord at C5 and C6 (arrow), and is associated with a large syrinx (dark intraspinal region extending rostral and caudal to the lesion). (D) Haematoxylin and eosin staining of a haemangioblastoma showing the lipid-laden stromal cells (arrows) distributed within a capillary network (arrowheads).

Histologically, they form papillary cystic regions filled with proteinaceous material (figure 5). Because of their adenomatous appearance and associated bone erosion, they were previously referred to as low-grade adenocarcinomas despite the absence of malignant features.

#### Treatment

Surgery is curative for completely excised tumours, and the preoperative level of hearing is usually preserved. Decisions about the timing of surgical treatment must allow for (1) the slow, but variable, growth of these tumours; (2) preoperative hearing level; (3) severity of vestibular symptoms; (4) possibility of hearing loss or facial nerve injury as a result of surgery; and (5) the possibility of bilateral tumours. The role of radiation therapy in the treatment of these tumours is unclear.

### Visceral lesions

#### Renal cell carcinomas and renal cysts

##### General features

Renal cell carcinomas are the major malignant neoplasm in von Hippel-Lindau disease and the primary cause of inherited renal cancer. These tumours are seen in 24–45% of patients, and adding renal cysts increases the finding of renal lesions to 60% (table 1).<sup>20,22</sup> The mean age at presentation is 39 years (table 1). Although small renal tumours in this disease tend to be low grade and minimally

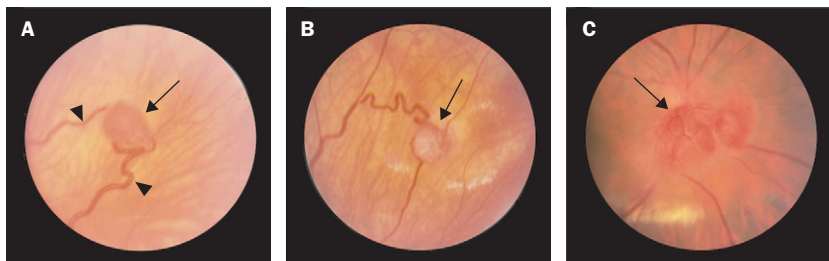
invasive,<sup>73</sup> their rate of growth varies widely.<sup>74</sup> Renal lesions are often multiple and bilateral. Walther and colleagues<sup>75</sup> estimated that 600 microscopic tumours and 1100 microscopic clear-cell-lined cysts might be present in the kidneys of some 37-year-old patients. Results of an investigation of 228 renal lesions in 28 patients, followed for at least 1 year, showed that transition from a cyst to a solid lesion was rare.<sup>76</sup> However, complex cystic and solid lesions can contain neoplastic tissue that frequently enlarges.<sup>73,76</sup>

##### Clinical, imaging, and histological findings

Renal cell carcinomas often remain asymptomatic for long intervals. Thus, serial imaging of the kidneys is useful for early diagnosis. Occasionally, the more advanced cases with these neoplasms can present with haematuria, flank pain, or a flank mass. Renal cysts in von Hippel-Lindau disease are typically asymptomatic and seldom need treatment. However, complex cysts need monitoring, as they often harbour solid components of renal cell carcinoma. Because of the frequent absence of early clinical symptoms and the importance of early detection, diagnosis during presymptomatic screening has the potential to enhance overall outcome.

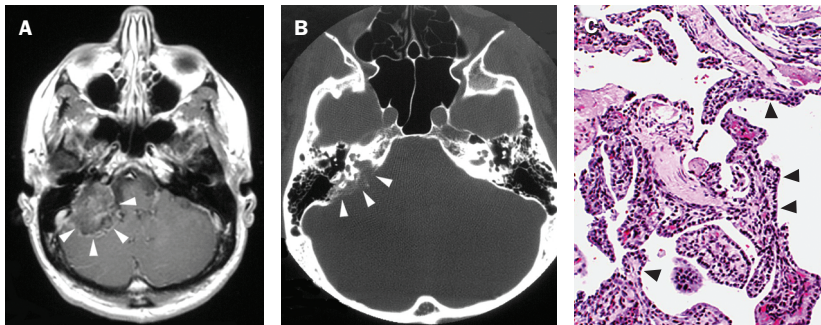
Contrast-enhanced abdominal CT is the standard for detection of renal involvement in the disease (figure 6). CT allows detection and quantification by size and number of renal cell carcinomas and cysts, allowing serial monitoring of individual lesions. Imaging is usually recommended in 3–5 mm sections, and before and after intravenous injection of contrast media. Precontrast and postcontrast MRI is an alternative method of detection for patients who have reduced renal function.

These carcinomas are yellow or orange and are encapsulated. They can be solid or a mixture of solid and cystic in appearance. Histologically, they are always of the clear-cell subtype (figure 6), and small carcinomas tend to be low grade.<sup>73</sup> Treatment recommendations can depend on tumour size.



**Figure 4: Ophthalmoscopic view of retinal haemangioblastomas**

(A) Peripheral retinal haemangioblastoma (arrow) with an enlarged vessel (arrowheads) in a 22-year-old woman. (B) Peripheral retinal haemangioblastoma (arrow) with fibrous changes, and hard exudates and retinal oedema in the surrounding region in a 24-year-old man. (C) Retinal haemangioblastoma (arrow) on the optic nerve head with yellow retinal hard exudates below it in a 32-year-old man.



**Figure 5: Imaging and histological characteristics of endolymphatic sac tumour in a 33-year-old man with right-sided hearing loss**

(A) Axial T1-weighted postcontrast MRI shows large heterogeneously enhancing tumour in the right mastoid region (indicated by arrows). (B) Axial CT scan through the same region showing the bony erosion of posterior petrous region that often occurs in these tumours (indicated by arrowheads). (C) Haematoxylin and eosin-stained section showing the typical histological features of this neoplasm, including cuboidal epithelium (arrowheads) in a papillary pattern.

#### Treatment

Some clinicians recommend nephron-sparing surgery for carcinomas that have a maximum diameter of 3 cm. Nephron or renal-sparing resection is designed to reduce the risk of metastasis while preserving kidney function. Walther and colleagues<sup>74</sup> reported a 10-year investigation of renal-sparing surgery, with a maximum tumour diameter of 3 cm. In patients who had surgery there was no evidence of metastases and no need for dialysis or kidney transplantation (median follow-up 60 months, n=52).

Percutaneous radiofrequency ablation or cryoablation of small carcinomas ( $\leq 3$  cm diameter) are experimental treatments that hold promise of being less invasive than other therapies.<sup>77-79</sup> Pavlovich and colleagues<sup>77</sup> reported the initial results of radiofrequency ablation of 24 renal tumours of 3 cm or less; 19 patients had renal cell carcinomas associated with von Hippel-Lindau disease, and two had hereditary papillary renal cancer. After 2 months' follow-up, CT showed that 19 of the 24 lesions were ablated. Other workers have successfully used percutaneous cryoablation guided by MRI to treat four patients who had a total of five renal tumours ranging in size from 2.8 cm to

5 cm.<sup>79</sup> Large carcinomas (greater than 3 cm) with bulky multifocal disease could carry an increased risk of metastases. Surgeons might recommend tumour enucleation or partial nephrectomy for such patients. In rare cases, in whom the kidney cannot be preserved, total nephrectomy might be the only option.

#### Phaeochromocytomas

##### General features

Phaeochromocytomas arise in 10–20% of patients with von Hippel-Lindau disease, but in a high percentage of affected members of some kindreds (type 2, see panel 2). The mean age at presentation is about 30 years (table 1).<sup>80</sup> Phaeochromocytomas in von Hippel-Lindau disease can be multiple and bilateral, and for some patients might be

the only manifestation of the disorder (type 2C). They can also arise as extra-adrenal paragangliomas in the glomus jugulare, carotid body, and periaortic tissues. 5% of all phaeochromocytomas are malignant.<sup>80</sup>

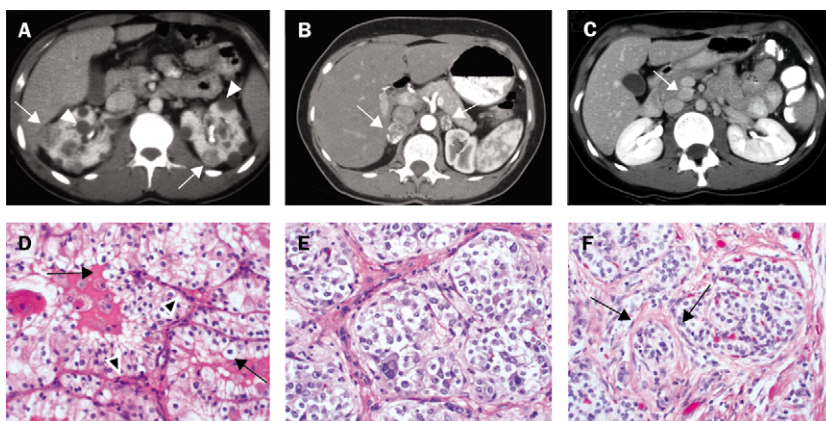
##### Clinical, imaging, and histological findings

Onset of phaeochromocytomas can take place before age 10 years, and can present as a hypertensive crisis in young children with von Hippel-Lindau. The signs or symptoms of phaeochromocytomas include intermittent or sustained hypertension, palpitations, tachycardia, headaches, episodic sweating, pallor, and nausea. Walther and colleagues<sup>80</sup> noted that 13 of 37 newly diagnosed patients (identified by screening affected kindreds) with phaeochromocytomas had no symptoms. Because of the early onset of these tumours and the frequent absence of signs and symptoms, screening for raised catecholamine values begins at about age 2 years especially in patients who have a family history of phaeochromocytomas (panel 1).

The diagnosis of phaeochromocytoma is based on laboratory and imaging studies. Functional tests for this disorder can be useful because they might show activity when imaging studies do not detect adrenal or extra-adrenal tumours. In addition to the 24 h urinary measurements of catecholamines, which could be falsely negative, measurement of plasma free metanephrines with reference ranges adjusted for age, is a sensitive method for detection of phaeochromocytomas.<sup>81,82</sup> Further assessment could include provocative testing with glucagon stimulation or clonidine suppression, or both.

Precontrast and postcontrast CT or MRI can detect adrenal masses (figure 6). However, identification of extra-adrenal phaeochromocytomas might need additional techniques. Meta-iodobenzylguanidine (MIBG) scintigraphy can detect extra-adrenal phaeochromocytomas and might confirm their catecholamine production. These tumours appear as red or orange encapsulated masses with foci of haemorrhage and necrosis.

Histologically, phaeochromocytoma cells arise from chromaffin cells of the adrenal gland, and have polyhedral to



**Figure 6: Axial postcontrast CT imaging and histological characteristics of various visceral tumours**

(A) Bilateral multifocal renal cell carcinoma with both solid (arrows) and cystic (arrowheads) disease in a 22-year-old man. (B) Bilateral phaeochromocytomas (arrows) with rim enhancement in the adrenal glands of a 29-year-old woman. (C) Pancreatic neuroendocrine tumour (arrows) in the head of the pancreas of a 26-year-old woman. (D) Renal cell carcinoma of the clear-cell subtype (arrows) with acinar and tubular architecture embedded in fibrovascular stroma (arrowheads). (E) Phaeochromocytomas are composed of chromaffin cells. The tumour cells are arranged in rounded clusters, separated by endothelial-lined spaces, and have vesicles containing norepinephrine and epinephrine. (F) Pancreatic neuroendocrine tumours show trabecular architecture, small nuclei, and abundant eosinophilic cytoplasm. Nests of tumour cells show focal nuclear atypia with surrounding stromal collagen bands (arrows).

fusiform morphology with vesicular nuclei, and granular, amphophilic, or basophilic cytoplasm (figure 6).

#### Treatment

For ideal perioperative management of patients with von Hippel-Lindau disease, an up-to-date assessment of the patient's overall condition should be done before they have surgery or go into labour. However, preoperative screening is especially important for detection of hidden pheochromocytomas because of the potential risk of a hypertensive crisis perioperatively. Treatment of pheochromocytomas is most often by surgical resection (preferably laparoscopically), and is increasingly done as part adrenalectomy or enucleation to preserve adrenal function.<sup>83</sup> Before surgery, pharmacological control with a combination of  $\alpha$  blockade and metyrosine blockade is often needed. Indications for surgery can include tumours with abnormal function, Meta-iodobenzylguanidine uptake, or tumour size greater than 3.5 cm.<sup>80</sup> In patients with von Hippel-Lindau disease and pheochromocytomas, early intervention with cortical-sparing adrenal surgery results in low recurrence rates and long-term corticosteroid independence.<sup>84</sup>

### Pancreatic neuroendocrine tumours and cysts

#### General features

Pancreatic neuroendocrine tumours arise in 8–17% of patients with von Hippel-Lindau disease.<sup>15,85,86</sup> Pancreatic cysts and serous cystadenomas occur with a prevalence of 17–56%.<sup>85,87</sup> Overall, 35–70% of patients have a pancreatic neuroendocrine tumour, cyst, or cystadenoma.<sup>87–89</sup> Distinguishing between a benign multicystic cystadenoma and a pancreatic neuroendocrine tumour can be difficult. The mean age at presentation for neuroendocrine tumours is 35 years, and for pancreatic cysts is 37 years.

#### Clinical, imaging, and histological findings

Pancreatic cysts in this disease are generally asymptomatic, and do not need treatment. Most of these tumours are non-functional. Thus, they are often clinically silent and routine periodic imaging of asymptomatic individuals is important for diagnosis of von Hippel-Lindau disease.

A pancreatic neuroendocrine tumour can be seen as an enhancing mass in postcontrast CT imaging done during the arterial (early) phase (later phase imaging might not clearly distinguish the tumour from surrounding healthy tissue) (figure 6, F). Once this tumour is identified with CT, pancreatic MRI can be used to confirm the diagnosis. Additional studies, including endoscopic ultrasound exploration in conjunction with somatostatin receptor scintigraphy, could be useful for diagnosis. Pancreatic neuroendocrine tumours are encapsulated and well circumscribed.

Histologically, they are formed from pancreatic islets and have been historically termed islet cell tumours. Although they are clinically non-functional, with immunohistochemistry they stain positive for pancreatic and gastrointestinal hormones (figure 6, F).<sup>90</sup>

#### Treatment

Treatment is by surgical resection, and the specific approach is determined by the location and size of the tumour. Tumours detected during imaging of asymptomatic periods, and resected on the basis of size have been successfully managed with no development of metastasis. Libutti and colleagues<sup>85,90</sup> recommend the following criteria for resection of these lesions: (1) no evidence of metastatic disease; (2) tumour size greater than 3 cm in the body or tail, or greater than 2 cm in the head of

the pancreas; or (3) the patient undergoing laparotomy for other lesions. Surgical resections can be done by enucleation, pylorus-preserving pancreaticoduodenectomy (Whipple's procedure), or part or total (rarely) pancreatectomy with replacement therapy. Tumours in the body and tail have been noted to be successfully managed with laparoscopy.<sup>90</sup>

Preservation of functional pancreas should be done with the malignant potential of the tumour in mind. In metastatic hepatic disease (the most common metastases), long-term control has been achieved by combinations of ablative therapy and isolated hepatic chemotherapeutic perfusion. Patients who do not meet the criteria for resection, have been successfully followed with CT at 12-month intervals.<sup>85,90</sup>

### Epididymal cystadenomas

#### General features

Epididymal papillary cystadenomas are seen in 25–60% of men with von Hippel-Lindau disease and can be multiple and bilateral.<sup>91–94</sup> The tumours are benign and typically appear in the teenage years. They arise from the epididymal duct, which is derived from the embryonic mesonephric duct.

#### Clinical, imaging, and histological findings

These cystadenomas are characteristically asymptomatic. The diagnosis is made by palpation and confirmed by ultrasound with sonographic criteria<sup>95</sup> that include (1) predominantly solid tumour greater than 10×14 mm, (2) occurrence in a man with von Hippel-Lindau disease, and (3) slow growth.

Epididymal cystadenomas appear solid but consist of multiple cysts (filled with a colloid-like material) and papillary fronds with a fibrovascular core. Histologically, the epithelium has clear-cell features similar to other lesions in the disease.

#### Treatment

Because these lesions are benign and typically symptomless, they are managed conservatively and treatment is reserved for the rare occurrence of symptoms. Ultrasonography can be used to monitor their growth over time.

### Broad ligament cystadenomas

#### General features

Papillary cystadenomas in the broad ligament have rarely been reported and are unrecognised in many women with von Hippel-Lindau disease.<sup>96–98</sup> The mean age of women at presentation and true frequency of cystadenomas in this disease is unknown. Gaffey and others<sup>97</sup> refer to the tumour as adnexal papillary cystadenoma of probable mesonephric origin, since the tumours are believed to arise from the remnant of the embryonic mesonephric duct. The earliest age at which this tumour has been diagnosed is 16 years, but in other reports, the age of onset is between 22 years and 46 years (table 1).<sup>96–98</sup>

#### Clinical, imaging, and histological findings

These lesions can be diagnosed by CT-imaging or ultrasonography. The tumours are grossly and histologically similar to epididymal cystadenomas.

#### Treatment

Because they are benign and typically asymptomatic, they can be managed conservatively. Treatment is reserved for the rare occurrences of symptoms. CT or ultrasonography can be used to document their size over time.

## Conclusion

The new insights into the underlying mechanisms of tumour formation, greater knowledge of the natural history of the various lesions associated with von Hippel-Lindau disease, and more precise diagnostic studies (laboratory and imaging) should lead to an improved quality of life and extend the life expectancy of affected individuals. The diverse multisystem effects of this disease need careful, selective, and coordinated planning to determine the treatment of individual lesions that will provide the best long-term management of these patients.

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