Learning objectives

- To review, illustrate and describe the broad spectrum of imaging features associated with VHL disease different manifestations.

- To discuss the most appropriate imagiologic screening investigation and management for patients with von Hippel Lindau (VHL) disease.

Background

VHL disease is a rare autosomal dominant inherited syndrome with high penetrance and variable expression, which involves inactivation of tumour suppressor gene on chromosome 3p25.5, resulting in a multisystemic disorder (1-3).

Prevalence of VHL disease is estimated to be between one of 31000 and one of 53000 (1).

Approximately 20% of cases of VHL disease are found in individuals without a family history, known as new mutations. An inherited mutation of the VHL gene is responsible for the remaining 80% of cases (2,3).

At present, according to the natural history of the disease, median survival in these patients is 49 years (1).

This syndrome includes various benign and malignant tumours such as hemangioblastomas of the central nervous system, endolymphatic sac tumours, renal cell carcinomas, pancreatic cysts and tumours, pheochromocytomas and epididymal cystadenomas, and other less common lesions (4).

The most common lesions of VHL disease according to prevalence are (5):

- Pancreatic cysts (50-91%)
- Cerebellar hemangioblastoma (44-72%)
- Renal cysts (59-63%)
- Retinal hemangioblastoma (45-59%)
- Renal cell carcinoma (24-45%)
- Spinal cord hemangioblastoma (13-59%)
- Pheochromocytoma (0-60%)
• Neuroendocrine tumour of the pancreas (5-17%)
• Serous cystadenoma of the pancreas (12%)
• Medullary hemangioblastoma (5%)
• Papillary cystadenoma of the epididymis (10-60% of male patients).

Death is usually caused by neurologic complications of cerebellar hemangioblastomas and renal cell carcinoma (4).

VHL germline mutations can be detected by a variety of tests performed on DNA. Because of the number of organs involved and the number of lesions that may be present, the high-risk gene carriers must undergo regular surveillance both clinically and radiologically (1-3).

Imaging plays a crucial role in the screening of gene carriers, due to the fact that most of the lesions are treatable. Thus, early detection allows opportune and more conservative therapy, which may enhance patient's quality and length of life.

In order to early detect VHL diseases typical abnormalities and to ensure its subsequent follow-up, different imaging modalities can be used, such as ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI).

Screening protocol for VHL disease by Leung et al (6):

• Annual blood pressure and neurological examination.
• Annual direct and indirect ophthalmoscopy from age 5 years, ± fluorescein angiography.
• Annual 24-hour measurement of the urinary vanillyl mandelic acid (VMA) level from age 10 years.
• Annual abdominal ultrasound from age 10 years.
• Baseline MR imaging of the brain and spine at age 20 years; low threshold for repeat if any symptoms/signs.
• Auditory questionnaire - if positive, audiogram. MRI if audiogram abnormal.

**Imaging findings OR Procedure details**

**Hemangioblastomas**

• Correspond to the most common tumour type in von Hippel-Lindau (VHL) disease (1, 7).
• Affect about 60-84% of patients (1,7).

• Are capillary-vessel-rich and well-circumscribed benign tumours (7).

• Occur within the cerebellum, brainstem, spinal cord, nerve roots and retina, and rarely above the tentorium (7).

• Do not invade locally or metastasize but can cause significant morbidity and mortality (7).

**Retinal Hemangioblastomas**

• Are among the most common and earliest detected VHL lesions - found in 45-59% of patients, with half of all cases being bilateral (1).

• Can occur in children aged <10 years (5% of all cases) (8) so, it is important to initiate ophthalmic surveillance in childhood.

• The average age at presentation is 25 years (8).

• Usually asymptomatic until complications arise (exudates, subretinal oedema, retinal detachment or glaucoma), causing loss of vision.

• They are histologically identical to the CNS hemangioblastomas (8).

• New lesions may develop quickly - frequent monitoring is essential.

• Typical Radiologic findings (6,8):

  • At no enhanced T1-Weighted MR imaging, lesions demonstrate higher signal intensity than normal vitreous.

  • When these lesions are found as contrast-enhanced CT or MRI, they normally are already large and patients usually present profound vision loss.

**CNS Hemangioblastomas (Figure 1, 2 and 3)**

• They are among the most common lesions associated with VHL disease: Cerebellum (44-72%) and spinal cord (13-59%) are the most common sites for hemangioblastoma development. Medullar hemangioblastomas occurs in 5% of cases and supratentorial lesions are less common (6,7,9).
• Only 5-30% of all cerebellar hemangioblastomas are attributed to VHL disease (7).

• 80% of spinal cord hemangioblastomas are attributed to VHL disease (8).

• Patients with VHL frequently have multiple hemangioblastomas along the craniospinal axis.

• Clinical presentation depends on the tumour location due to pressure on adjacent structures or through haemorrhage (ex headache, ataxia, incoordination, nausea/vomiting, sensory loss, weakness, hyperreflexia) (8).

• These tumours may be solid, cystic, haemorrhagic, or mixed (7).

• Typical Radiologic findings (6, 9):

• Hemangioblastomas enhance avidly on post contrast CT and T1-weighted MRI sequences.

• To best delineate peritumoural oedema and/or cysts associated with hemangioblastomas, T2-weighted or fluid-attenuated inversion-recovery (FLAIR) magnetic resonance sequences are used.

• When associated with peritumoural cysts, hemangioblastomas often have the classic ‘cyst with mural nodule’ appearance; however, these tumours can also less frequently develop complex or intratumoural cysts.

![Fig. 1: Cerebellar Hemangioblastomas - in the right cerebellum, sagittal pre (a) and post (b) gadolinium-enhanced T1-Weighted and axial (c) T2-Weighted MRI images shows a predominantly solid nodule iso/hipointense at nonenhanced T1-Weighted that enhance avidly on post-gadolinium T1-Weighted sequences, with a central cystic component.](image-url)
**Fig. 2:** Cerebellar hemangioblastomas - sagittal (a) and axial (b, c) gadolinium-enhanced T1-weighted MRI images showing multiple solid nodules that enhance avidly on postcontrast T1-weighted sequences.  
**References:** Serviço de Radiologia, Centro Hospitalar Lisboa Norte, Hospital de Santa Maria - Lisboa/PT

**Fig. 3:** Spinal cord hemangioblastoma - sagittal (a) and coronal (b) gadolinium-enhanced T1-weighted MR images showing spinal cord hemangioblastomas (arrows).  
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**Endolymphatic Sac Tumours**

- VHL disease increases the risk of developing Endolymphatic Sac Tumours (1).
- Occur in 11% of VHL disease patients (the prevalence of bilateral tumours is reported to be 7%) (10).
- Usually located in the posterior part of the petrous temporal bone and can erode nearby bone (10).
- They are local invasive, but do not metastasize (10,11).
- Present with hearing loss, tinnitus, vertigo and facial nerve palsy is seen once the tumour becomes > 3cm (7,11).
- Surgery is curative, can relieve vertigo and may prevent progression of hearing loss (11).

- Typical Radiologic findings (6, 8, 10):
  - Intratumural calcification on CT scan.
  - Hyperintense focal signals on T1-weighted (noncontrast-enhanced) MRI.
  - Heterogeneous signal on T2-weighted MRI scan.

**Renal Cysts and Tumours (figure 4, 5, 6, 7)**

- Renal involvement in VHL consists of multiple, usually small and bilateral lesions which may include benign cysts, atypical cysts, cystic renal cell carcinomas, and solid renal cell carcinomas (8, 12, 13).
- Renal cysts occur in 59-63% of VHL patients (12, 13).
- Renal cell carcinoma (RCC) occur 24-45% of VHL patients (12, 13).
- Renal lesions are bilateral in about 75% of VHL patients (12, 13).
- In VHL disease the presentation average age for RCC is between 30 and 36 years (occur at a younger age than in the general population) (12, 13).
• Serial imaging is important to detect suspect solid tumours or any malignant transformation of seemingly benign cysts - if left untreated, RCC carries a poor prognosis and metastasizes widely (6).

• When associated with VHL disease, RCC can be either multicentric and/or solid hypervascular masses and/or complex cystic masses with mural nodules and/or thick septa (13);

• Typical Radiologic findings (6, 8, 12, 13):
  • US is useful to distinguish cystic from solid lesions and may be preferred for screening (allows a reduction of the amount of radiation exposure during lifetime).
  • CT is preferred in cases of suspicious or equivocal US findings.
  • CT is more sensitive than US to detect lesions smaller than 2 cm.
  • Cysts demonstrate little or no wall enhancement, but solid components show contrast captation.
  • The best MRI sequences to study renal cysts and tumours are fast T2-weighted imaging or contrast-enhanced T1-weighted imaging with fat suppression. Simple cysts are hypointense on T1-weighted images and hyperintense on T2-weighted images, with no enhancement after administration of gadolinium contrast material. Complex or solid lesions enhance on postcontrast T1-weighted images and may also demonstrate a low-signal intensity pseudocapsule on T2-weighted images.
Fig. 4: Renal Cysts and Renal Cell Carcinoma - US image (a) shows a mixture of simple and complex cysts. The simple renal cyst has a thin, imperceptible wall and anechoic fluid content. The complex renal cyst has thick wall and septa. The second US image (b) shows a suspicious lesion with mixed echotexture, that represents a renal cell carcinoma.

References: Serviço de Radiologia, Centro Hospitalar Lisboa Norte, Hospital de Santa Maria - Lisboa/PT

Fig. 5: Simple and complex renal cysts - axial CT images show two complex cysts on the right kidney that have thick septa that enhance post contrast. In the left kidney there are multiple renal cysts that have thin walls and no septa or enhancement with IV contrast.

References: Serviço de Radiologia, Centro Hospitalar Lisboa Norte, Hospital de Santa Maria - Lisboa/PT
Fig. 6: Renal Cell Carcinoma - axial (a) and coronal (b) contrast-enhanced CT scan showing a solid heterogeneous and enhancing lesion in the left kidney. Note the presence of a pancreatic cyst (a).

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Fig. 7: Renal Cell Carcinoma - axial (a) and coronal (b) T2-weighted MR images show a solid Renal Cell Carcinoma of heterogeneous signal intensity. Note the pseudocapsule surrounding the tumor. Axial (a) MR images show the presence of a pancreatic cyst.

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Pancreatic Cysts and Tumours (Figure 8)

- Occur in 0-77% of patients (14).
- Present at the average age of 35 years (14).
- Pancreatic involvement by VHL disease includes: simple cysts (50-91%), serous microcystic adenomas (12%), adenocarcinomas (rarely) and neuroendocrine tumours (5-17%) (4, 8, 14).
- Most pancreatic cystic lesions are asymptomatic and diagnosed only in screening imaging. They may be the only abdominal manifestation of VHL disease and thus, its recognition permits earlier diagnosis. Usually, there is no significant progression of cystic pancreatic lesions, which allows conservative therapy (4, 8, 14).

- Typical Radiologic findings (6, 14):
  - Cystic lesions are commonly detected with US or CT. These modalities are similar in terms of sensitivity and specificity. Therefore, US is adequate for screening purposes, whilst CT is used for suspicious lesions. The walls of simple cysts enhance poorly or not at all.
  - Microcystic adenomas are usually well circumscribed, with numerous small cysts normally < 2 cm. Enhancement occurs at the periphery of these microcysts. The great number of small cysts at US may appear solid due to acoustic interfaces. It may be impossible to distinguish a group of benign cysts from a microcystic adenoma. This has no clinical implications, as microcystic adenoma is a benign lesion.
Fig. 8: Pancreatic cysts - axial (a) and coronal (b) enhanced CT scan shows multiple pancreatic cysts, which virtually replace the pancreatic parenchyma. T1-weighted (c) and T2-weighted (d) MR images demonstrate multiple pancreatic cysts that are high signal on T2 and low signal on T1.

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Neuroendocrine Pancreatic Tumours

- Neuroendocrine pancreatic tumours, or islet cell tumours, occur in 5-17% of VHL patients (4, 13).
- Frequently occur in VHL patients that also have pheochromocytomas (13).
- When associated with VHL disease, neuroendocrine pancreatic tumours have low rates of malignancy and metastasis (<10%), so an expectant therapeutic can be adopted (13).
• Most of these tumours are non-functional and slow growing lesions and do not cause symptoms (13).

• Seldom, when these lesions are functional, they can secrete insulin, glucagon, gastrin and somatostatin, causing symptoms and thus allowing early diagnosis (13).

• In larger tumours, areas of calcification, necrosis and cystic degeneration may be present (13).

• Typical Radiologic findings (6, 13):
  • US - Neuroendocrine pancreatic tumours have well defined margins, round morphology and frequently are hypoechoic relative to pancreatic parenchyma.
  • CT - these tumours are homogeneous and hypo or isoattenuating when compared to the normal pancreatic parenchyma. Typically, there is intense contrast enhancement in the arterial phase.
  • MRI - these lesions are hypointense on T1-weighted MR images and hyperintense on T2-weighted images.

**Pheochromocytomas (Figure 9)**

• Pheochromocytomas have a prevalence that can vary from 0% to 60% (4).

• In families with a high prevalence of these lesions, there is a lower incidence of cerebellar hemangioblastoma and RCC (4).

• Pheochromocytomas associated to VHL disease appear at a younger age, are usually multiple, ectopic (15%-18%) and can be bilateral (50%-80%) (4).

• Only a very low proportion corresponds to malignant lesions (4).

• They arise from the neural crest and may produce elevated levels of catecholamines in the serum and urine. Nevertheless, many lesions are asymptomatic and results of biochemical tests are normal (4).

• The symptoms/signs are headaches, palpitations, episodic sweating, pallor and nausea; intermittent or sustained hypertension. Although, there can be no symptoms (4, 8).

• Typical Radiologic findings (4, 6, 8):
• The typical appearance at CT is a solid or complex cystic mass that may have areas of necrosis, haemorrhage, and calcifications. Marked enhancement is also typically seen, although small areas of the tumour may remain with low attenuation.

• At MR imaging, 95%-100% of lesions have low or intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images and show marked gadolinium enhancement.

![Pheochromocytoma - axial contrast-enhanced CT scan shows heterogeneous enhancing solid adrenal lesions on both sides.](image)

**Fig. 9:** Pheochromocytoma - axial contrast-enhanced CT scan shows heterogeneous enhancing solid adrenal lesions on both sides.

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**Papillary Cyst-adenomas of the Epididymis**

• Common in men with VHL disease (found in 10%-60%) (4, 6, 13).
• If there are bilateral cyst-adenomas of the epididymis, it is pathognomonic of VHL disease (6, 13).

• Usually located in the head of the epididymis, but may also involve the spermatic cord (6, 13).

• Asymptomatic; may be found on palpation (6, 13).

• Usually no treatment is required because they don't have malignant potential (6, 13).

• Typical radiologic findings (6, 13):
  
  • Diagnosis/monitoring done with US.
  
  • In US they are mixed echotexture, with both solid and cystic components; Calcifications may be present.

  • Ductal ectasia within the rete testis and testicular atrophy may be present.

Images for this section:

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![CT Image of Renal Cysts and Renal Cell Carcinoma](image)

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![CT Image of Simple and Complex Renal Cysts](image)
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Conclusion

Imaging plays a key role in the screening and long-term surveillance of VHL gene carriers, enabling early detection and treatment of abnormalities and enhancing the patients length and quality of life.

References


Personal Information