CT and MR imaging aspects in von Hippel Lindau disease

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Abstract

Von Hippel Lindau is an multisystem autosomal dominant disorder that causes tumors of the central nervous system (brain, retinal, and spinal cord hemangioblastomas), endolymphatic sac tumors, renal cell carcinomas, renal cysts, pheochromocytomas, pancreatic cysts and tumors, and epididymal cystadenomas. In this review we describe the major semiological computed tomography and magnetic resonance imaging findings of this pathological entity.

Key words: von Hippel Lindau disease, computed tomography, magnetic resonance imaging

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Introduction

Von Hippel–Lindau (VHL) disease is a rare dominant hereditary multisystem disorder that is characterized by development of a variety of benign and malignant tumors. Inheritance is autosomal dominant with high penetrance and variable expression (1,2). The prevalence is estimated to be between 1/31,000 and 1/53,000. About 40 different lesions in 14 different organs have been described (5). These include retinal and central nervous system (CNS) hemangioblastomas, endolymphatic sac tumors, renal cysts and tumors, pancreatic cysts and tumors, pheochromocytomas, and epididymal cystadenomas (3).

Identification of patients with VHL disease allows accurate genetic counseling. Early detection of central nervous system and visceral tumors in patients with von Hippel Lindau disease enhance the length and the quality of life (1-3).

Learning objectives
1. Describe genetics and clinical manifestations of VHL disease.
2. Recognize the imaging appearances of various manifestations of VHL disease.
3. Discuss computed tomography and magnetic resonance imaging aspects of VHL disease and the role of imaging investigations.

Genetics

The inheritance of VHL disease is autosomal dominant; there is a 50% chance of inheriting the VHL gene from a carrier. The gene has high penetrance but variable expression. The VHL gene is a tumor suppressor gene; thus, when both copies of the gene are inactivated by mutation or loss, cell growth is unregulated and tumors in multiple organs result. The location of the tumor suppression gene was isolated to chromosome 3p25.5 (1,2,8,9).

Diagnostic criteria

The diagnostic criteria for VHL disease include the following:
1. more than one CNS hemangioblastoma,
2. one CNS hemangioblastoma and visceral manifestations of VHL disease, and
3. any manifestation and a known family history of VHL disease (3-6).

Imaging methods

Imaging like computed tomography (CT) and magnetic resonance (MR) imaging plays a key role in identification of abnormalities and in subsequent follow-up of lesions (3,4,7).

Imaging findings

Various imaging findings are correlated with retinal and central nervous system (CNS) hemangioblastomas, endolymphatic sac tumors (19,20), renal cysts and tumors, pancreatic cysts and tumors, pheochromocytomas, and epididymal cystadenomas (7).

Central nervous system abnormalities

Symptoms of cerebellar lesions include headache, vertigo, ataxia, vomiting, nystagmus, and ninth cranial nerve palsy (16). Focal spinal pain is the most common symptom of spinal cord hemangioblastome. In some cases presentation can be late with increased intracranial pressure due to obstructive hydrocephalus and impending spinal cord compression. Hemangioblastomas (HBs) are rare tumors located in the cerebellum in 3/4 of cases (Fig.1), whereas 1/4 are located inside the spinal canal (9-13). HBs account for 1–5% of all spinal cord tumors. Seventy-five percent of spinal HBs are intramedullary, usually located in the posterior half of spinal cord, and another 10–15% have combined intramedullary-extradural components. Hemangioblastomas are highly vascular lesions that readily enhance with contrast material. They may be solid, cystic, hemorrhagic, or mixed (14-18). They are often cystic with a solid enhancing mural nodule. The MR imaging characteristics are low to medium signal intensity on T1-weighted images and high signal intensity on T2-weighted images. The most useful sequence for detection of these lesions is unenhanced and contrast-enhanced T1-weighted imaging.
Extramedullary-intradural HBs are often attached to the dorsal spinal cord pia, and, in some cases, lesions can arise solely from nerve roots (Fig.2). Extradural tumors are very rare. Most of the intramedullary or extramedullary spinal HBs are reported in cervical or thoracic location. The lesions reported in the conus medullaris (14) or in the extramedullary compartment adjacent to the conus medullaris (15) are rare. Tumors of the cauda equine are uncommon, and lesions of the filum terminale are extremely rare. HBs of the lower spinal region are highly vascular tumors predominantly fed by the anterior spinal artery also known as the artery of Adamkiewicz.

Treatment of CNS hemangioblastomas involves surgical resection of symptomatic tumors, with preoperative arterial embolization for extensive spinal cord tumors. Hemangioblastomas associated with VHL disease which are difficult to manage surgically, has led to an interest in use of gamma knife therapy (18).

Renal Masses

Renal cysts occur in 59%–63% of patients, and renal cell carcinoma (RCC) in 24%–45% (3). Lesions are bilateral in as many as 75% of patients (22). Renal tumors do occur at a younger age (mean, 30–36 years) in VHL disease than in the general population (23). Serial imaging is important in detecting any malignant transformation of benign cysts. Studies have shown that cysts commonly grow over time. However, some involute leaving small scars, and in others the solid component may enlarge (24). There is no correlation between cyst size and number and malignant potential. The renal cystic lesions vary from simple cysts to hyperplastic cysts and cysts containing clear cell carcinoma; solid tumors have also been described (22,23). The full pathologic spectrum may occur in a single kidney.

CT is useful in cases of multiple renal cysts, where the renal architecture has been distorted and is difficult to analyze with ultrasound (3).
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).

Nephron-sparing surgery or, more recently, radiofrequency ablation can be used to maintain renal function (24,25).

**Pheochromocytomas**

Pheochromocytomas develop in fewer than 30% of families with von Hippel-Lindau disease. The typical appearance at CT is a solid or complex cystic mass that may have areas of necrosis, hemorrhage, and calcifications (3). Marked enhancement is also typically seen, although small areas of the tumor may remain of low attenuation. If an adrenal lesion is discovered at CT, MR imaging is then performed, as it is superior to CT in evaluating ectopic sites of pheochromocytoma (3). 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.

**Pancreatic Masses**

The frequency of pancreatic involvement in von Hippel-Lindau disease is 15–77% (3). Lesions include simple pancreatic cysts (91%), serous cystadenomas (12%), neuroendocrine tumors (7–12%), and combined lesions (11%). Pancreatic cystic lesions are benign, whereas neuroendocrine tumors can be malignant (Fig. 5). Pancreatic adenocarcinoma and hemangio-blastome have also been described in von Hippel-Lindau disease (26-28).

Pancreatic cysts. In most patients, pancreatic cysts are asymptomatic. However, in some instances they can cause local compression of adjacent organs, vessels, and the common bile duct. CT and MRI show multiple pancreatic cysts with no enhancement after contrast injection.

Serous Cystadenomas. On CT, these masses typically appear as microcystic, well-defined cystic loculi, central calcifications, enhancement around microcysts after injection of contrast media, and larger cysts on the periphery of the mass. On MRI, serous cystadenomas have high signal intensity on T2-weighted images. Serous cystadenomas can be difficult to differentiate from simple cysts at imaging, and the visualization of enhancing septa favors the diagnosis of microcystic adenoma. However, the differential diagnosis is not important because these lesions require no treatment.

Pancreatic neuroendocrine tumors. Pancreatic neuroendocrine tumors have a low prevalence in von Hippel-Lindau disease. They are usually nonfunctional and asymptomatic, often multiple, with a slow rate of growth, and have no particular pancreatic location. A low incidence of malignancy has been reported, but metastases can occur in lesions larger than 3 cm. Pancreatic neuroendocrine tumors appear on CT (3,26) and MRI as hypervascular pancreatic masses, with possible necrotic changes and heterogeneous enhancement in large lesions.

The functional pancreatic neuroendocrine tumors commonly secrete peptides such as insulin, glucagon, gastrin, and somatostatin; thus, clinical presentation is early, when the tumors are small (27). The treatment is surgery, including proximal or distal pancreatectomy, depending on the location and the size of the lesions.
Other Abdominal Lesions
Liver cysts and cystadenomas of the epididymis and of the broad ligament have been associated with von Hippel-Lindau disease (28,29,30).

Screening of Abdominal Lesions in von Hippel-Lindau Disease
The following tests are recommended for screening of abdominal lesions: ultrasound yearly, beginning at 10 years old; this may be followed up with CT or MR imaging, depending on the US findings. Some centers perform annual CT or MR imaging to screen the kidneys. Patients also receive adrenal screening, which consists of 24-hour measurement of urinary vanillyl mandelic acid level annually. No imaging is warranted unless this is abnormal. For CNS screening, baseline MR imaging of the brain and spine is performed at age 20 years followed by annual neurologic examinations (3). Ophthalmic screening consists of annual direct and indirect ophthalmoscopy from the age of 5 years (3).

Conclusions
Manifestations of von Hippel Lindau disease are protean. Imaging plays a key role in the identification of visceral and central nervous system abnormalities, in the follow-up and long-term surveillance screening. Early detection of tumoral lesions enables more conservative therapy to be performed and may enhance the patient’s length and quality of life.

References
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**Rezumat**

Von Hippel Lindau este o boală multisistemică ereditară cu transmitere autozomal dominantă care determină apariția de tumori ale sistemului nervos central (hemangioblastoame cu localizare cerebrală, retiniană și spinală) tumori de sac endolimfatic, carciinoame renale, chisturi renale, feocromocitoame, chisturi și tumori pancreatice și chistadenoame de epididim. În acest articol descriem caracterele semiologice majore în evaluarea computer tomografică și prin rezonanță magnetică ale acestei entități patologice.

**Cuvinte cheie:** boală von Hippel Lindau, computer tomografie, imagistică prin rezonanță magnetică