INTRODUCTION

Von Hippel-Lindau (VHL) disease is an autosomal dominant hereditary disease that is characterized by the formation of tumors. The disease is related to germline mutations in the VHL gene, which acts as a tumor suppressor gene and is located on the short arm of chromosome 3, at locus 3p25–26(1,2). The estimated incidence of VHL disease is 1:36,000 population, with penetrance > 90% as of 65 years of age(3).

The VHL disease typically manifests in young adulthood, with an average age at onset of 33 years, and predisposes affected patients to the development of benign and malignant tumors, mainly in the central nervous system (CNS) and viscera(4). The average life expectancy of patients with VHL disease is 49 years, the most common causes of death being clear cell renal carcinoma and hemangioblastoma(5). Most of the lesions related to the disease are treatable, and, according to various protocols, monitoring is recommended.

VHL disease can be classified by clinical phenotype, each of which correlates with a specific genotype(1): type 1—low risk for pheochromocytoma and high risk for hemangioblastomas, clear cell renal carcinoma, cysts, and pancreatic neuroendocrine tumors; type 2A—high risk for pheochromocytoma and low risk for clear cell renal carcinoma; type 2B—high risk for pheochromocytoma and clear cell renal carcinoma; and type 2C—high risk only for pheochromocytoma. Characteristic CNS tumors in VHL
disease include retinal, cerebellar, and spinal cord hemangioblastomas, as well as endolymphatic sac tumors\(^{(3)}\).

A clinical diagnosis of VHL disease can be considered under the following circumstances: in a patient with a family history of VHL disease and at least one of the tumors characteristic of the disease (retinal hemangioblastoma, CNS hemangioblastoma, clear cell renal carcinoma, pancreatic neuroendocrine tumor, or endolymphatic sac tumor); in a patient with two or more retinal or CNS hemangioblastomas; in a patient with a retinal or CNS hemangioblastoma, plus at least one of the visceral tumors characteristic of VHL disease, excluding renal and epididymal cysts\(^{(1)}\). Genetic testing for germline mutations in the VHL gene can also confirm the diagnosis. In this context, imaging examinations play an important role in the diagnosis and follow-up of patients with VHL disease.

**INTRACRANIAL MANIFESTATIONS**

VHL disease is characterized by CNS hemangioblastomas, which affect 60–80% of patients with the disease. Hemangioblastomas are benign tumors (classified as grade I tumors by the World Health Organization) that are multifocal, being characterized histologically by a large vascular network and vacuolated stromal cells, which can be quite voluminous. Hemangioblastomas can present as nodular or solid/cystic lesions\(^{(3)}\), affecting mainly the cerebellum and spinal cord\(^{(6)}\). The evolution of such lesions typically includes phases of growth and phases of stability, the average age at the onset of symptoms being 33 years. The symptoms vary depending on the expansile effect and the tumor site\(^{(1,3)}\).

**CEREBELLAR HEMANGIOBLASTOMAS**

Among individuals with VHL disease, the reported prevalence of cerebellar hemangioblastoma ranges from 44% to 72%. Approximately 5–30% of all cerebellar hemangioblastomas are attributed to VHL disease\(^{(6)}\). Affected patients may present with ataxia, dysmetria, headache, diplopia, vertigo, or vomiting. Such symptoms occur because the cysts related to a hemangioblastoma grow much faster than does the primary tumor itself and have significant expansile effects\(^{(1)}\). The location in the cerebellar hemispheres may be related to the development of ataxia and dysmetria. Cerebellar lesions caused by VHL disease are close to the pial surface and are often cystic, with thin walls and eccentric solid components\(^{(6)}\). Computed tomography (CT) shows homogeneous cysts with well-defined walls and an eccentric mural nodule that, on unenhanced images, is isodense to the surrounding tissue, whereas it shows intense enhancement on contrast-enhanced images. On magnetic resonance imaging (MRI), hemangioblastomas have a cystic component with a signal that is hypointense on T1-weighted images and isointense or hyperintense on T2-weighted images (Figure 1). The solid component is classically characterized by facilitated diffusion and intense contrast enhancement\(^{(1)}\). Prominent flow voids related to tumor vascularization can often be seen. When a cerebellar hemangioblastoma is identified, it is important to actively look for other foci of enhancement throughout the neuraxis, given that the presence of other hemangioblastomas suggests VHL disease\(^{(2,6)}\). Hemangioblastomas present abundant vascularization due to increased expression of vascular endothelial growth factor\(^{(7)}\), which explains the elevated relative cerebral blood volume seen in perfusion sequences of these tumors (Figure 2).

**HEMANGIOBLASTOMA OF THE SPINAL CORD**

Hemangioblastoma of the spinal cord is seen in 13–59% of patients with VHL disease. Although any segment of the spinal cord can be affected, hemangioblastomas are
most common in the thoracic and cervical segments\(^6\).

The predominant symptoms, which include hyperesthesia, weakness, ataxia, hyperreflexia, pain, incontinence, and even quadriplegia, are related to radiculopathy and myelopathy. Unenhanced CT scans show a nodule in the spinal cord that, on unenhanced images, is isodense to the surrounding tissue and, on contrast-enhanced images, shows intense enhancement. On MRI, a hemangioblastoma of the spinal cord tends to be hypointense on T1-weighted images and hyperintense on T2-weighted images, often with regional flow voids (Figure 3). These tumors also show intense enhancement on contrast-enhanced MRI scans and are accompanied by syringomyelia in 50–100% of cases\(^1\).

**METASTASIS**

In patients with VHL disease, metastasis to the CNS most commonly originates from a clear cell renal carcinoma (Figure 4). Less commonly, metastases originate from a pheochromocytoma/paraganglioma or from a metastatic neuroendocrine tumor\(^8\).

**RETINAL HEMANGIOBLASTOMAS**

Retinal hemangioblastomas are common in VHL disease, being seen in up to 60% of patients. The mean age at presentation is 25 years, although it is estimated that up to 5% of cases occur in patients under 10 years of age\(^3\). Bilateral involvement is seen in up to 50% of cases. In up to 6% of patients, retinal hemangioblastomas cause complications such as macular exudation, exudative or tractional retinal detachment, vitreous hemorrhage, neovascular glaucoma, and amaurosis. Histopathological findings include fenestrated endothelial cells, pericytes, and lipid-rich foam cells in the stroma. The diagnosis is confirmed by ophthalmoscopy, which reveals a tumor with tortuous vessels and optic disc edema. Contrast-enhanced CT and MRI may reveal nodular retinal lesions with enhancement (Figure 5), with or without retinal detachment\(^1\).
ENDOLYMPHATIC SAC TUMORS

Endolymphatic sac tumors occur in up to 15% of cases of VHL disease, the mean age at presentation being 22 years. Such tumors are bilateral in up to 30% of patients\(^1,6\). Endolymphatic sac tumors are highly vascularized papillary cystadenomas that grow in the posterior region of the petrous portion of the temporal bone\(^3\). These tumors arise from the vestibular aqueduct and are benign, although they are locally invasive and can erode adjacent structures, such as the semicircular canals and the cochlea. The symptoms are hearing loss, tinnitus, dizziness, and facial nerve palsy. A CT scan with bone window settings demonstrates a bone lesion with a moth-eaten appearance in the petrous portion of the temporal bone\(^3\). On contrast-enhanced images, an endolymphatic sac tumor presents intense enhancement. On MRI, such tumors show a signal that is hyperintense on T1-weighted images (denoting the presence of hemorrhagic/proteinaceous content) and heterogeneously hyperintense on T2-weighted images. Contrast-enhanced T1-weighted images demonstrate intense enhancement of solid tumor components\(^1,6\), as illustrated in Figure 6.

FOLLOW-UP PROTOCOLS

All patients with VHL disease are predisposed to the development of benign or malignant lesions. Even if asymptomatic, such patients should be followed to detect new lesions and to monitor the progression of known lesions. Follow-up evaluations focus on hemangioblastomas (including retinal hemangioblastomas), endolymphatic sac tumors, pheochromocytomas, clear cell renal carcinomas, and pancreatic cystadenomas, as well as lesions of the epididymis and broad ligament of the uterus, and can be tailored to individual patient needs. Table 1 summarizes
current recommendations of the VHL Alliance Consensus\(^{(9)}\).

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