Von Hippel-Lindau disease

General information

Key concepts

● disorder with hemangioblastomas (HGB) primarily of cerebellum, retina, brainstem & spinal cord, as well as renal cysts/tumors, pheochromocytomas (among others)

● autosomal dominant, due to inactivation of tumor suppressor gene on 3p25

● expression and age of onset are variable, but ≈ always manifests by age 60

● mean age of developing HGBs is at least 10 years younger than sporadic HGBs

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The German ophthalmologist Eugen von Hippel first described angiomas in the eye in 1904.

Arvid Lindau described cerebellar angiomas and spine in 1927.

The term von Hippel-Lindau disease was first used in 1936, however, its use became common only in the 1970s.

Patients with VHL disease commonly develop cerebellar hemangioblastomas, which are frequently multiple.

von Hippel–Lindau (VHL) disease is a rare, autosomal dominant genetic condition that predisposes individuals to benign and malignant tumors. The most common tumours found in VHL are central nervous system and retinal hemangioblastomas, clear cell renal carcinomas, pheochromocytomas, pancreatic neuroendocrine tumours, pancreatic cysts, endolymphatic sac tumors and papillary cystadenoma of the epididymis.

Epidemiology

Von Hippel-Lindau disease epidemiology.

Classification

Subtypes of VHL

Type I: any manifestation of VHL (typically hemangioblastoma & renal cell carcinoma) except pheochromocytoma.

Type IIA: pheochromocytoma is characteristic. Renal cell carcinoma is rare.

Type IIB: high risk of hemangioblastoma, renal cell carcinoma and pheochromocytoma.

Type IIC: risk of pheochromocytoma only (without risk of hemangioblastoma or renal cell carcinoma).

VHL disease can be subdivided according to the clinical manifestations, although these groups often correlate with certain types of mutations present in the VHL gene.

Clinical features

Von Hippel-Lindau disease clinical features.

Genetics

Von Hippel–Lindau disease genetics.

VHL protein

The regulation of HIF1α by pVHL. Under normal oxygen levels, HIF1α binds pVHL through 2 hydroxylated proline residues and is polyubiquitinated by pVHL. This leads to its degradation via the proteasome. During hypoxia, the proline residues are not hydroxylated and pVHL cannot bind. HIF1α causes the transcription of genes that contain the hypoxia response element. In VHL disease, genetic mutations cause alterations to the pVHL protein, usually to the HIF1α binding site. The VHL protein (pVHL) is involved in the regulation of a protein known as hypoxia inducible factor 1α (HIF1α). This is a subunit of a heterodimeric transcription factor that at normal cellular oxygen levels is highly regulated. In normal physiological conditions, pVHL recognises and binds to HIF1α only when oxygen is present due to the post translational hydroxylation of 2 proline residues within the HIF1α protein. pVHL is an E3 ligase that ubiquitinates HIF1α and causes its degradation by the proteasome. In low oxygen conditions or in cases of VHL disease where the VHL gene is mutated, pVHL does not bind to HIF1α. This allows the subunit to dimerise with HIF1β and activate the transcription of a number of genes, including vascular endothelial growth factor, platelet-derived growth factor B, erythropoietin and genes involved in glucose uptake and metabolism.

Tumors associated with Von Hippel-Lindau disease

see Tumors associated with Von Hippel-Lindau disease.

Diagnosis

Von Hippel-Lindau disease diagnosis.

Treatment

Von Hippel-Lindau disease treatment.

Outcome

The lifespan of patients with Von Hippel-Lindau disease is decreased. 30–50% die of renal cell carcinoma (RCC). Metastases from RCC and neurologic complications from cerebellar hemangioblastoma are the primary causes of death. Metastases respond poorly to chemotherapy and XRT.

Case reports

von Hippel-Lindau disease case reports.