Neurosurgical Manifestations of VHL

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Disclosures

- NONE

- Beau

- Abi
von Hippel-Lindau Syndrome

- Rare (~1/40,000) autosomal dominant multisystem neoplastic disorder due to inactivation of the von Hippel–Lindau tumor suppressor also known as pVHL on chromosome 3p25-26
- pVHL is a protein that, in humans, is encoded by the VHL gene – a two-hit suppressor gene
- Mutations of the VHL gene are associated with VHL syndrome

Structure of pVHL (based on PyMOL rendering of PDB 1lm8 - an open source molecular visualization system created by Warren Lyford DeLano)
Von Hippel-Lindau Syndrome

- Von Hippel-Lindau syndrome (VHL) is a dominantly inherited familial cancer syndrome predisposing to a variety of malignant and benign tumors of the eye, brain, spinal cord, kidney, pancreas, and adrenal glands.
- A germline mutation of this gene is the basis of familial inheritance of VHL syndrome.
- Individuals with VHL syndrome inherit one mutation in pVHL that causes the protein's normal function to be lost or altered.
- Sporadic mutation in the second copy of pVHL over time can lead to tumor formation.
- Requires comprehensive screening and follow-up of individuals and their families.
The main action of pVHL is thought to be its E3 ubiquitin ligase activity that results in specific target proteins being 'marked' for degradation such as hypoxia inducible factor 1a (HIF1a), a transcription factor that induces the expression of angiogenesis related factors.

HIF is necessary for tumor growth because most cancers demand high metabolic activity and are only supplied by structurally or functionally inadequate vasculature.

Activation of HIF allows for enhanced angiogenesis, which in turn allows for increased glucose uptake.

In the normal cell with active VHL protein, pVHL directs the polyubiquitination of HIF1A, ensuring that this protein will be degraded by the proteasome.

The loss of pVHL activity results in an increased amount of HIF1a, and thus increased levels of angiogenic factors, including VEGF and PDGF, which lead to unregulated blood vessel growth, one of the prerequisites of tumor formation.

von Hippel-Lindau Syndrome
von Hippel-Lindau Syndrome

Characterized by development of tumors

- retinal angiomas
- hemangioblastomas of brain and SC
- clear cell renal carcinomas
- pheochromocytomas
- pancreatic cystadenomas
- endolymphatic sac tumors of the middle ear
von Hippel-Lindau Syndrome

Hemangioblastoma

- benign tumor - WHO grade 1
- symptoms depend on tumor location and size
- can be asymptomatic
- cystic lesion with very vascular mural nodule in brain (most often cerebellum) and/or spinal cord
- cyst wall lined with non-neoplastic compressed cerebellum/SC
- cure requires surgical removal of entire mural nodule – may leave cyst wall
- residual nodular component can lead to fatal hemorrhage
- inoperable tumors can be treated successfully with stereotactic radiosurgery (SRS) – small solid tumors respond best
• 15-year-old white male
• Chief complaint: “blurred vision”
• Eye exam by optometrist at OSSIP - multiple retinal angiomas
• Past medical/surgical histories otherwise negative
• Family and Social histories noncontributory
• Visual acuity: R eye 20/50, L eye 20/20
• 3 retinal capillary angiomas on the right with R macular edema
• Neurologic exam otherwise normal
Cerebellar Hemangioblastoma
Spinal Hemangioblastoma
Spinal Hemangioblastoma
Spinal Hemangioblastoma
Take home message: comprehensive screening and follow-up of individuals and their families are key components of management of VHL syndrome.