

Von Hippel-Lindau (VHL) Syndrome: A Critical Insight

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ABSTRACT

Von Hippel-Lindau (VHL) syndrome is a rare genetic neoplastic disorder, arising from germline mutations in the VHL gene, characterized by the development of visceral cysts, specific benign and malignant tumors in multiple organ systems that have subsequent potential for spiteful change. It is caused by point mutations or deletions in a tumor suppressor gene. A tumor suppressor gene is the one which keeps cells from growing and dividing too rapidly in an uncontrolled way. Mutations in this gene prevent production of the VHL protein or lead to the production of an abnormal version of the protein. An altered or missing VHL protein cannot effectively regulate cell survival and division. As a result, cells grow and divide uncontrollably to form tumors and cysts that are characteristic of Von Hippel-Lindau syndrome. Although there is great variation in the clinical presentation, those who have a mutated gene are at greatly increased risk of developing spinal hemangioblastoma, renal cell carcinoma (RCC), retinal hemangioblastoma, cerebellar hemangioblastoma, pheochromocytoma, pancreatic and renal cysts, endolymphatic sac tumors, hemangiomas of the adrenals, liver and lungs, and papillary cystadenoma of the epididymis or broad ligament. The age at which the tumors present ranges from early childhood to the seventh decade of life. Early diagnosis, screening of family members and lifelong surveillance of VHL patients is recommended.

Keywords: Hemangiomas, Pheochromocytoma, Stromal, Ophthalmoscopy, Polycythemia

INTRODUCTION

Von Hippel-Lindau syndrome is an autosomal dominantly inherited multi-systemic cancer disease predisposing to a variety of neoplasm (characterized by the formation of tumors and fluid-filled sacs called cysts in different parts of the body). Melmon and Rosen (1964) introduced the term 'Von Hippel-Lindau' syndrome and described large kindred with multiple features of the disorder ^[1]. The incidence of von Hippel-Lindau syndrome is estimated to be 1 in 36,000 individuals. The inheritance is autosomal with high penetrance. Most people with VHL syndrome inherit an altered copy of the gene from an affected parent. However, in 20% of the cases, the

altered gene is the result of a new mutation that occurred during the formation of reproductive cells (eggs or sperms) or very early in development ^[2]. Males and females are equally affected. Unlike most autosomal dominant conditions, in which one altered copy of a gene is sufficient to cause the disorder, two copies of VHL gene must be altered to trigger tumor and cyst formation in Von Hippel-Lindau syndrome. A mutation in the second copy of the VHL gene occurs during a person's lifetime in certain cells within organs such as the brain, retina and kidneys ^[3]. Almost everyone who inherits one VHL mutation will eventually acquire a mutation in the second copy of the

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gene in some cells, leading to the features of Von Hippel-Lindau syndrome.

Types

* Type 1 (without pheochromocytoma)

Type 1A (only without pheochromocytoma)

Type 1B (without pheochromocytoma and protection from renal cell carcinoma)

* Type 2 (with pheochromocytoma)

Type 2A (with pheochromocytoma and hemangioblastoma)

Type 2B (with pheochromocytoma and renal cell carcinoma)

Type 2C (with isolated pheochromocytoma, without hemangioblastoma or renal cell carcinoma)

Clinical manifestations: The diagnosis is usually made on clinical grounds. The finding of a single retinal or cerebellar hemangioblastoma, pheochromocytoma or RCC is considered sufficient to justify the diagnosis ^[4]. Tumors called hemangioblastomas are characteristic of Von Hippel-Lindau syndrome. These growths are made of newly formed blood vessels. Microscopically, hemangioblastoma consist of large polygonal stromal cells enmeshed in a capillary network. They are usually cherry red in colour.

CNS HEMANGIOBLASTOMAS

It is a chief feature of VHL occurring mostly in

- Cerebellum
- Spinal cord
- Brain stem

The tumor usually grows inside the parenchyma of cerebellum, brain stem or spinal cord; it is attached to the pia mater and gets its rich vascular supply from the pial vessels ^[5].

Signs and symptoms of cerebellar hemangioblastoma can include

- Increased intracranial pressure and limb ataxia

- Headache
- Slurred speech
- Nystagmus
- Positional vertigo
- Labile hypertension (without pheochromocytoma)
- Vomiting
- Wide-based gait

Patients with spinal cord lesions most frequently present with pain, followed by signs of segmental and long-track dysfunction due to progressive compression of the spinal cord ^[6]. Patients with hemangioblastoma of the brain stem present with a long history of minor neurological symptoms that, in most cases, are followed by sudden exacerbation, which may necessitate immediate neurological intervention ^[7]. In some patients of VHL disease, CNS hemangioblastomas may produce erythropoietin-like substances, resulting in polycythemia (usually clinically asymptomatic) at the time of diagnosis.

RETINAL ANGIOMAS (HEMANGIOBLASTOMAS)

Most common presenting feature of VHL disease, histopathologically similar to CNS hemangioblastoma, is associated with mainly thin-walled, capillary-like or slightly larger, blood vessels that are separated by plump, vacuolated and foamy stromal cells ^[8]. Ophthalmoscopy typically reveals a dilated feeder artery and draining vein.

Retinal angiomas may develop within the retina or optic nerve. However, in rare cases, they may develop in the posterior pole (1%) and optic disc (8%) ^[9]. The lesions, if untreated, will gradually grow, bleed and leak serous fluid that will finally detach the retina ^[10]. It mainly includes the cumulative risk of

- Visual loss and
- Sight-threatening complications such as
 - *Exudation
 - *Retinal traction
 - *Haemorrhage

Vision loss in patients with retinal hemangioblastoma may be a result of the macular edema that accompanies lesions that may be located in the periphery or at the optic disc.

The symptoms of retinal detachment are

- Flashes of light
- Spots in the vision (floaters)

Eye pain

Light sensitivity

Vision loss

Headache

RENAL CELL CARCINOMA (RCC)

It is a type of kidney cancer accounting for the main cause of death in VHL disease. The tissue of origin of RCC is the proximal renal tubular epithelium^[11]. Recent advances in understanding genetic changes associated in kidney tumor formation have led a new pathologic classification of RCC into five different types:

1. Clear cell type (65% of RCC)
2. Papillary cell type (Chromophil) (15% of RCC)
3. Chromophobe cell type (10% of RCC)
4. Oncocytoma (5% of RCC)
5. Unclassified cell type (5% of RCC): Sarcomas, collecting duct tumors, etc^[12].

Symptoms include

- Abdominal pain and swelling,
- Back pain,
- Blood in the urine,
- Swelling of the veins around a testicle,
- Flank pain and
- Weight loss.

Other symptoms may include excessive hair growth in females, pale skin, vision problems, anaemia (resulting from depression of erythropoietin), hypertension, hypocalcaemia, sleep disturbances and recurrent fevers^[13]. RCC is difficult to treat and rarely cured once it has

spread beyond the kidney and current therapies have limited efficacy.

PHEOCHROMOCYTOMA

It is a rare catecholamine-secreting tumor of the medulla of the adrenal glands. The diagnosis can be established by measuring amount of catecholamine and metanephrines in plasma (blood) or through a 24-hour urine collection^[14]. Imaging by computed tomography of the head, neck, chest and abdomen can help localize the tumor.

They may cause no symptoms, but in some cases, they are associated with

- Severe headaches
- Chest pain
- Excess sweating
- Sleeping difficulty
- Dangerously high blood pressure that may not respond to medication

Patients may feel warm and have pallor of the face. Body perspiration and cool, moist hands and feet may also be found. A mass may be palpable in the neck or in deep palpation of the abdomen. Deep palpation of the abdomen may produce a typical paroxysm^[15]

PANCREAS

Another common feature, pancreatic tumors are solid non-secretory islet cell tumors best detected by contrast enhanced MRI with early arterial phase imaging. Little is known about the origin of pancreatic cysts in general. Approximately, pancreatic cysts occur in 70% of VHL patients^[16]. Based on preclinical studies, cilia loss in ductal cells is probably an important early event in pancreatic cyst development.

OTHER FEATURES

Some other rare features found sometimes in VHL patients include:-

- Endolymphatic sac tumors (ELST), which can be detected by MRI or CT imaging.

- Tinnitus, hearing loss and vertigo may occur in many cases.
- Parasympathetic paragangliomas (characterized by germline mutations in succinate dehydrogenase subunit genes).
- Epididymal cystadenomas occur in 60% of the males with VHL disease ^[17].
- Broad ligament cystadenomas rarely occurs.

MANAGEMENT

Von Hippel-Lindau syndrome is a complex disorder. Its management is associated with the treatment of the various clinical aspects associated with it.

- For CNS hemangioblastomas, stereotactic radiotherapy may be an alternative to conventional neurosurgery for non-cystic small hemangioblastomas though adverse reactions may occur.
- Most retinal angiomas respond well to laser photocoagulation or cryotherapy.
- External beam radiotherapy (EBRT) and vitreoretinal surgery are also a useful option in the treatment of retinal angiomas ^[18].
- For renal cell carcinoma, nephrectomy (surgery to remove all or a part of the affected

kidney) is recommended. Other useful options are chemotherapy, immunotherapy and radiation therapy.

- Treatment of pheochromocytoma is with surgical removal but it is a high-risk procedure because intraoperative manipulation of the tumor may induce excessive catecholamine excretion, resulting in a life threatening hypertensive crisis.
- Laparoscopic adrenalectomy has been shown to be a useful technique, alternative to surgery, for treating pheochromocytoma, in patients with tumors smaller than 7 cm.
- Pancreatic neuroendocrine tumors are managed by surgical resection, depending on size and location of tumor ^[19].
- For endolymphatic sac tumors, surgery is curative; can relieve vertigo and may prevent progression of hearing loss.
- Since Von Hippel-Lindau is a hereditary disease and is transmitted in an autosomal dominant manner, family members of patients with these syndromes should be educated about familial multiple-cancer syndrome, and genetic counseling should be offered to the patients and family members.

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