Von Hippel-Lindau disease

Key facts

- Von Hippel-Lindau (VHL) disease is a rare, inherited disorder caused by genetic variants in the *VHL* gene.
- VHL causes cysts and tumours to develop in various organs from late childhood.
- VHL disease most frequently affects the eyes, cerebellum, kidneys, spinal cord, adrenal gland or pancreas.
- Retinal angiomas (enlarged blood vessels) are often the initial manifestation of VHL disease and can cause vision loss if not treated.
- Renal cell carcinoma occurs in about 70% of individuals with VHL, necessitating surveillance.
- Although VHL disease can have serious complications, if these are detected early through regular screening, they can usually be treated successfully.
- VHL is inherited in an autosomal dominant manner. The children of an individual with VHL have a 50% (one-in-two) chance of inheriting the genetic alteration.
- VHL is very variable, often presenting with different complications and at varying ages, even within the same family. However, there is a tendency for phaeochromocytomas to run in particular families.

Clinical features

- In the eye, enlarged blood vessels (angiomas) can occur on the retina. These do not cause any problems when small, however, if an angioma is not detected and treated, it may enlarge, leak or bleed, damaging the retina and eventually impairing vision.
- Benign tumours called haemangioblastomas can occur in the cerebellum or spinal cord, along with cysts that can expand. If they occur in the cerebellum, individuals can present with symptoms of headache and unsteadiness when walking. Haemangioblastomas in the spinal cord can cause pain or numbness.
- Renal cystic disease may occur as part of VHL disease but is usually benign and asymptomatic. Renal cell carcinoma (RCC) is more common. If detected early, RCC can be easily removed, but can become invasive without early treatment.
- Cysts, and occasionally neuroendocrine tumours, can also occur in the pancreas, though tumours tend to be benign.
- In some patients, a benign tumour called a phaeochromocytoma can develop in the adrenal gland. This produces adrenaline and other hormones, and may cause high blood pressure.
- Rarely, a small tumour may occur in the inner ear, often causing hearing difficulties (tinnitus and hearing loss).
- Epididymal cysts can also feature as part of VHL disease.

Genetic basis

- VHL occurs due to a genetic variant in one of the two copies of the *VHL* gene.
- The *VHL* gene is a tumour suppressor gene important in a variety of cell growth processes, including the development of new blood vessels.

- In most cases, it is possible to identify the precise gene variant causing VHL, which enables pre-symptomatic testing to identify family members at risk and guide screening.
- A variety of variant types occur (deletion, frameshift, nonsense, missense and splice-site mutations) that either reduce gene expression, or result in the production of abnormal VHL protein.
- VHL is inherited in an autosomal dominant manner: the children of an individual with VHL have a 50% (one-in-two) chance of inheriting the genetic variant and VHL.
- Often, the gene alteration is inherited from a parent, but occasionally an individual with VHL is the first to have the gene variant in the family due to a new ('de novo') variant. Their children still have a 50% (one-in-two) chance of inheriting the variant and therefore, the disease.

Diagnosis and genetic testing

- Diagnosis is usually achieved through identification of a disease-causing genetic variant in the *VHL* gene. A genetic variant can be identified in around 90% of those with VHL, however, some families can have a clinical diagnosis of VHL even when a genetic variant cannot be identified.
- Genetic testing is indicated in families with two or more lesions suggestive of VHL (retinal angioma, haemangioblastomas, multiple renal or pancreatic cysts, renal cell carcinoma, phaeochromocytoma, and endolymphatic sac tumours).
- Genetic testing may sometimes be suggested if one isolated tumour type occurs, but should be discussed with a specialist.
- Genetic testing of the *VHL* gene should be offered to individuals with suspected VHL to identify the specific genetic variant in the family. Pre-symptomatic testing for the specific gene variant can then be offered to at-risk family members to identify those who have VHL and require screening.
- Testing in childhood should be offered due to the early development of lesions and/or the requirement for childhood screening.
- Pre-implantation genetic diagnosis of VHL is available in specialised fertility units.

Clinical management

- Clinical management is best done by a multidisciplinary team that includes: renal physicians, urologists, clinical geneticists, endocrinologists, radiologists and clinical and medical oncologists.
- Screening for tumours and other complications is important to aid treatment. A person who has no symptoms but has a parent with VHL disease should also be offered regular screening, unless the family-specific variant can be identified, and the person is shown not to have this specific genetic variant through genetic testing. If a patient who has VHL disease, or has a relative with it, develops symptoms, they should seek medical advice as a matter of urgency and should always mention the family history of VHL.
- The exact type and timing of screening investigations will vary according to individual circumstances, but usually includes:
    - an annual eye examination by an ophthalmologist from an early age;
    - an annual MRI or CT scan of the kidneys from the age of 16;
    - an annual 24-hour urine or blood test (for hormone levels) from childhood; and
    - a brain and spinal MRI scan every few years, usually from the age of 16 (if a haemangioblastoma is found, it will usually only be removed if it is causing symptoms).
- These investigations are usually continued throughout life, although the screening protocol can be modified according to an individual's risk.

- The complications of VHL disease are easier to treat if detected early. Treatments include:
  - » laser treatment of retinal angiomas;
  - » surgical removal of haemangioblastomas in the cerebellum or spine if they are causing difficult symptoms;
  - » care from a renal physician and/or urologist for patients with renal cystic disease, though the renal cysts may not require treatment;
  - » surgical removal or occasionally less invasive treatment (for example, cryotherapy) of an RCC if detected; and
  - » surgical removal of a phaeochromocytoma if detected.

Direction to further reading, guidelines and patient groups

- VHL Alliance
- VHL UK Ireland

This information is intended for educational use and was current in January 2020. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and Imperial College Healthcare NHS Trust.