Von Hippel-Lindau disease

Key facts

- Von Hippel-Lindau (VHL) disease is a rare, inherited disorder caused by a genetic alteration (or mutation) 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 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% chance of inheriting the genetic alteration.
- VHL is very variable, often presenting with different complications and at different ages in different individuals, 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. When small these do not cause any problems. However, if an angioma is not detected and treated it may enlarge, leak or bleed, damaging the retina and eventually impair 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 they usually present with symptoms of headache and unsteadiness on walking. Haemangioblastomas in the spinal cord can cause pain or numbness. These can be detected by MRI scan.
- Renal cystic disease may occur in 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 tumours, can also occur in the pancreas. Pancreatic 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.
- Epididymal cysts can also feature in VHL disease.

Diagnosis

- 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 tumors). Genetic testing may sometimes be suggested if one isolated tumour occurs, but should be discussed with a specialist.
- Diagnosis is usually through identification of a disease-causing genetic alteration in the VHL gene. A genetic alteration can be identified in around 90% of those with VHL. However, some families have a clinical diagnosis of VHL even when a genetic alteration cannot be identified.

Genetic basis

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

Clinical management

- Screening for tumours and other complications is important to aid treatment. 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 scan of the kidneys from the age of 16;
  - an annual 24-hr urine test (for hormone levels) from childhood; and
  - a brain scan every few years usually from 16 years; however, a cerebellar haemangioblastoma 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.
- If a patient who has VHL disease, or has a relative with it, develops symptoms they should seek medical advice sooner and should always mention the history of VHL.
- A person who has no symptoms but has a parent with VHL disease should also be offered regular check-ups unless the family specific mutation can be identified and the person is shown not to have this specific genetic alteration through genetic testing.
- The complications of VHL disease are easier to treat if detected early. Treatments include:
- retinal angiomas may be treated by laser;
- haemangioblastomas in the cerebellum or spine may be removed surgically if they are causing difficult symptoms;
- renal cysts may not need treatment but patients with renal cystic disease should be under the care of a renal physician; and
- if an RCC or phaeochromocytoma is detected, it will generally be surgically removed.

Genetic testing

- Genetic testing of the VHL gene should be offered to individuals with suspected VHL to identify the specific genetic alteration in the family wherever possible.
- Pre-symptomatic testing for the specific gene alteration 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 in some cases and the requirement for childhood screening.

This information is intended for educational use and was current in March 2015. For clinical management, it is recommended that local guidelines and protocols are used.