Osler-Weber-Rendu Syndrome

Synonyms: hereditary haemorrhagic telangiectasia, HHT, HHT1 and Rendu-Osler-Weber disease

Hereditary haemorrhagic telangiectasia (HHT) is also known as Osler-Weber-Rendu syndrome. The condition is characterised by vascular dysplasia leading to telangiectasia. Epistaxis and gastrointestinal bleeding are frequent complications of mucosal involvement. There are also often arteriovenous malformations (AVMs), particularly of lungs, liver and brain.[1]

Genetics

It is part of a group of disorders inherited in an autosomal dominant fashion. Most cases are due to mutations in the endoglin (HHT1) or ACVRLK1 (HHT2) genes.[2] There is evidence of genetic heterogeneity. It is inherited with high penetrance, as 97% have symptoms.[3]

Epidemiology

The population prevalence is between 1 in 5,000 and 1 in 8,000.[4]

Presentation

Age-related penetrance is seen in HHT.[2] It does not present at birth but commonly presents with recurrent epistaxis, usually in the teenage years. People with the condition develop mucocutaneous lesions, usually involving the nasal mucosa, lips and tongue. These lesions are sharply demarcated red-purple macules, papules or spider-like lesions comprising a mat of tortuous vessels. These can also occur in the conjunctiva, upper respiratory tract, gastrointestinal (GI) tract, bladder, vagina, bronchi, brain and liver. Cutaneous telangiectasias are often not evident until between 20 and 30 years of age. Unfortunately, due to the relatively low prevalence of the condition, it is frequently underdiagnosed.[2]

Other associated features

- In the GI tract, abnormalities are present in 11-40%. There may be telangiectasia and AVMs causing acute haemorrhage or chronic slow bleeding with resulting iron-deficiency anaemia. In one series, 33% had a history of haematemesis or melaena.[5]
- In the respiratory system, AVMs occur in 30-50% of people with HHT. These pulmonary AVMs are direct communications between the pulmonary arteries and pulmonary veins without an interposed capillary bed. These may present as dyspnoea, cyanosis, bruits, high-output heart failure, clubbing and paradoxical cerebral emboli that may cause stroke and cerebral abscess. They can also lead to haemoptyisis and haemothorax.[6]
- In the liver, AVMs can cause high-output cardiac failure or cirrhosis due to hepatic vascular abnormalities, fibrosis, and portacaval shunts. In one series, patients with HHT were investigated using CT scanning. 74% had vascular abnormalities but only 8% were symptomatic.[7]
- In the central nervous system, AVMs, cavernous angiomas and aneurysm may result in headache, seizures or epilepsy, intracranial haemorrhage and stroke.
- Lesions of the skin do not usually develop until the 20s. They affect the hands and wrists in 41% and the face in 33%. They do not tend to be a serious problem with regard to haemorrhage.
- Vascular malformations of the urinary tract are rare, in one series being present in just 2 of 324 cases.[3]

Differential diagnosis

- CREST syndrome (= Calcinois, Raynaud's disease, (o)Esophageal dysmotility, Sclerodactyly, Telangiectasia).
- Von Willebrand's disease.

Investigations

- Capillary microscopy (examining the capillary pattern of the fingernail; this can be useful in screening for HHT, as most patients have detectable abnormalities before development of other signs).
- CT, MRI scanning and angiography (for example, pulmonary and cerebral angiography) are used to identify lesions.[6]

Diagnosis

The diagnosis is made if at least three of the following are present:[9]

- Epistaxes
- Telangiectasia
- Visceral lesions
- Appropriate family history
Genetic testing can be undertaken to identify the specific mutation in the index case. This can then be used to investigate other family members.\[^{2}\]

**Associated diseases**

- Osler-Weber-Rendu type 2 (HHT2) - is a distinct but very similar disorder, mapped to chromosome 12. HHT2 is associated with pulmonary arterial hypertension.\[^{10}\]
- Juvenile polyposis with HHT syndrome has been reported in a few families.\[^{11}\] There is inherited haemorrhagic telangiectasia associated with juvenile polyposis coli and colorectal cancer. The gene defect is on chromosome 18.
- A third type has also been described that is mapped to chromosome 5 and is called HHT3.\[^{12}\]

**Management**

- Optimal management is improved with early diagnosis, based on clinical findings.
- Acute haemorrhage may require treatment including blood transfusion and attempts to stem the flow.
- Surgical or laser ablation may be required as an emergency or elective procedure. AVMs may need embolisation, ligation of the blood supply or resection.
- Septoplasty of the nose may be required.
- Liver transplantation or stereotactic intracranial radiosurgery may be indicated.
- However, a recently published paper concluded that in adults with unruptured brain AVM, interventional therapy appears to worsen outcomes compared to medical management.\[^{13}\]
- Pregnancy in HHT is associated with an increased risk of life-threatening complications.\[^{2}\]
- For some years it has been noticed that oestrogens seem to have a beneficial effect on the lesions.

**Oestrogen therapy**

Oestrogens provoke squamous metaplasia of the epithelium. Oestrogens with progestogens (oral contraceptives) are beneficial in women of reproductive years.\[^{14}\] Anti-oestrogen, such as tamoxifen, is also beneficial although the term anti-oestrogen may be naive. Tamoxifen is an oestrogen antagonist on the breast but has agonist properties for bone and endometrium. The selective oestrogen receptor modulators (SERMs) also have mixed effects. There is no evidence as to whether lower doses of oestrogens, as are used in hormone replacement therapy, are also beneficial.\[^{14}\]

There is evidence that not everyone will respond and there may be advantage in taking a nasal biopsy and assessing the tissue for oestrogen-binding sites.\[^{15}\] Therapy may be offered on the basis of receptor status.

Oestrogens also have benefit when used in men but predictable adverse events will occur.
Complications
As above, haemorrhage is the major concern. The effects depend upon site and size.

Cirrhosis occurs in a small number.

Prognosis
Usually there is no effect on lifespan unless there is severe haemorrhage, although cirrhosis may shorten life.

Historical notes
The condition was first described by Henry Gawen Sutton (1836-1891) in 1864. The following year, Benjamin Babington (1794-1866), in a paper in The Lancet, noted that it was familial. Henri Jules Louis Marie Rendu (1844-1902) was the first to differentiate the condition from haemophilia (1896). Osler (1849-1919) raised the profile of the disease by subsequently describing a family with nosebleeds, multiple telangiectasias of the skin and mucous membranes, in 1901. F. Parkes Weber (1863-1962) described later cases of angiomas.

Further reading & references
10. Telangiectasia, Hereditary Hemorrhagic, Type 2, HHT2; Online Mendelian Inheritance in Man (OMIM)
11. Juvenile Polyposis/Hereditary Hemorrhagic Telangiectasia Syndrome, JPHT; Online Mendelian Inheritance in Man (OMIM)
12. Telangiectasia, Hereditary Hemorrhagic, Type 3, HHT3; Online Mendelian Inheritance in Man (OMIM)

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