Hereditary Hemorrhagic Telangiectasia (HHT, Osler-Weber-Rendu disease) — Symptoms and Diagnosis

See online here

Hereditary hemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu-Disease (OWRD) is a rare autosomal dominant disorder that affects blood vessels and consequently multiple systems resulting in a tendency to bleed. Also known as vascular dysplasia, the condition is more or less diagnosed clinically and has a variable prognosis depending on prompt recognition and severity. However, there is no cure. This article will throw light on clinical features of the disease as well as its diagnosis to aid in identification and management.

Definition of HHT

HHT as genetic disorder

HHT or OWRD (Osler-Weber-Rendu disease) is an autosomal dominant genetic disorder that involves abnormal blood vessel formation throughout the body. It is a rare disorder with variable age of presentation. It is characterized by:

- Epistaxis
- Mucocutaneous telangiectases
- Arteriovenous malformations (AVMs)

**Image**: “A very large arteriovenous malformation in the left hemisphere (on the right in this image) of the brain.” by The Armed Forces Institute of Pathology (AFIP). License: Public Domain

**Epidemiology of HHT**

**Frequency of HHT**

HHT occurs with **equal frequency** in both males and females. While the geographic distribution of the disease is wide, it is more commonly seen in the **Whites**. Being asymptomatic, the prevalence may be underestimated, but the overall prevalence is **1-2 cases per 10,000 populations** in North America. It may occur in children, but is more common at the time of puberty or during adulthood.

**Etiology of HHT**

**Causes of HHT**
As already mentioned, it is an autosomal dominant disorder, with 5 genetic types and homozygous condition being incompatible with life. **Mutations involving TGF-B** signaling are responsible for the disorder:

- Mutations of ENG (HHT type 1): account for 80–85 % cases along with type 2
- ALK1 Mutations (HHT type 2)
- Chromosome 5 mutation
- SMAD4/MADH4

A child born to an HHT patient has a 50 % chance of developing it and almost all of them inherit it from their parent. Rarely does it develop in a child of unaffected individuals. See the right figure for the inheritance pattern.

**Pathophysiology of HHT**

A defect in TGF-B superfamily receptor results in **abnormal architecture of vessels** and **consequent malformations and aneurysms**. This combined with abnormal repair results in **lesions**. Dilated vessels manifesting as telangiectasis are most commonly a result of:

- Endothelial cell degeneration and junction defects
- Perivascular connective tissue weakness

The gene expression profiles of vascular endothelial cells grown from HHT patients revealed dysregulation of genes involved in:

- Angiogenesis
- Cytoskeletal integrity
- Cell migration
- Proliferation
- NO synthesis
Signs and Symptoms of HHT

It is generally considered that clinical manifestations of the condition are not present since birth and develop with the passage of time and increasing age. The frequency of these features is as follows.

**Spontaneous and recurrent Epistaxis** is the most common feature present (> 90 %). Varying in frequency and severity, it mostly develops till adolescence and in children it’s a strong indication of AVMs in lungs or brain, requiring intervention.

![Image: "Tongue telangiectases in hereditary hemorrhagic telangiectasia" by Herbert L. Fred, MD and Hendrik A. van Dijk – Images of Memorable Cases: Cases 115 & 116. Licensed under Attribution via Commons]

**Skin Telangiectases** occurs in > 75 %. Telangiectases are dilated blood vessels on hands, tongue, face, lips and GI tract. The skin lesions are often referred to as red spots and it’s important to differentiate this characteristic manifestation from benign red spots.

**Pulmonary or Hepatic involvement (AVMs)** appear in > 30 % and may include:

- Dyspnea
- Exercise intolerance
- Cyanosis
- Hypoxemia
- Secondary polycythemia
- Jaundice
- Esophageal varices
- High-cardiac output failure symptoms

**GI bleeding** is > 15 % and there’s also the chance of CNS lesions (involving migraine headaches, strokes, brain abscess).

**Diagnosis of HHT**

The clinically driven diagnosis is based on Curacao criteria and make use of the following 4 criteria:

- Epistaxis
- Telangiectasis
- Visceral lesions
- Family history (first degree relative)
In contrast to petechiae (small spots caused by hemorrhage), the **red color of telangiectasis disappears** while pressing a transparent spatula onto the skin. While lab tests may not confirm the diagnosis, they are certainly helpful in complication identification and assessment. These include:

- CBC: reduced hemoglobin, iron-def anemia or polycythemia
- Coagulation profile: deranged in severe hepatic involvement
- Urinalysis: hematuria
- Stool: blood presence
- LFTs: elevated enzymes
- Oximetry < 96 % requires further testing
- ABGs (screening test for pulmonary AVMs)

### Diagnosing HHT with radiology

<table>
<thead>
<tr>
<th>Test</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Chest radiography</td>
<td>May reveal enlarged mass of arteries and veins and/or peripheral non-calcified coin lesion</td>
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<tr>
<td>Transthoracic contrast echocardiography (TTCE)</td>
<td>Pulmonary AVMs</td>
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<tr>
<td>Barium enema</td>
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<tr>
<td>Contrast enhanced MRI</td>
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<td>Angiography</td>
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<td>Ultrasound and contrast radiography</td>
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<td>Endoscopy</td>
<td>Reveal telangiectasis</td>
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<td>Barium enema</td>
<td>Suspected ulcers and neoplasms</td>
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<tr>
<td>Helical CT</td>
<td>Delineating lung and brain AVMs</td>
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<tr>
<td>Abdominal CT</td>
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Genetic testing has a higher sensitivity in confirmed cases. A biopsy shows:

- Dilated capillaries
- Focal dilatation of post-capillary venules (telangiectasis)
- Fully developed lesions lacking intervening capillary bed
- New vessel formation
- Thickened dilated vessel walls in dermis
Differential Diagnosis of HHT

Diseases similar to HHT

With the presence of three criteria, the diagnosis is definite. But the following conditions should be ruled out as well:

- Ataxia-telangiectasia
- CREST syndrome
- Pediatric Syphilis
- Rosacea
- Rothmund-Thomson syndrome
- Scleroderma
- Cockayne syndrome
- Actinic keratosis

Therapy of HHT

Treatment of HHT

Management of HHT aims at reducing hemorrhage and sequelae of malformations. While mild cases require no treatment, the treatment options for moderate and severe cases include:

**Epistaxis treatment:**

- Iron supplementation
- Humidification
- Packing
- Transfusion
- Electrocautery
- Septal dermoplasty

**Pulse dyed laser treatment** for telangiectasis

**GI bleeding management:**

- Estrogen-progesterone therapy
- Transfusion
- Aminocaproic acid
- Endoscopic photoablation

**AV malformations** are managed by:

- Surgical resection (> 1.5 cm)
- Embolization
- Liver transplantation

**Long-term monitoring**

Progression and Prognosis of HHT

Screening and appropriate management tend to increase the overall life expectancy. The prognosis depends on the disease severity and especially hepatic, pulmonary
and CNS involvement.

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