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

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 a variable age of presentation. Its characteristic symptoms include:

- Epistaxis
Mucocutaneous telangiectases
- Arteriovenous malformations (AVMs)

“Telangiectasia” and “arteriovenous malformation” both occur from a direct connection between an artery and a vein while bypassing the capillary system. They are pathologically-distinct terms. Telangiectasias occur on mucocutaneous surfaces, such as the skin, gastrointestinal (GI) mucosa, or upper aerodigestive tract. AVMs occur in internal organs, such as the liver, lungs, and brain.

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 Caucasians. Since it is asymptomatic, its prevalence may be underestimated. However, the overall prevalence is 1-2 cases per 10,000 people in North America. It may occur in children but is more common at puberty or during adulthood.

Etiology of HHT

Causes of HHT
As already mentioned, it is an autosomal dominant disorder. There are five genetic types and homozygous conditions that are incompatible with life. **Mutations involving Transforming Growth Factor Beta (TGF-B)** signaling are responsible for the following disorders:

- Endoglin Gene (ENG) mutations (HHT type 1): account for 80–85% cases along with type 2
- Activin receptor-like kinase-1 (ALK1) mutations (HHT type 2)
- Chromosome 5 mutation
- SMAD4 (also known as MADH4)

Almost all HHT cases are congenital. A child born to a parent with HHT has a 50% chance of developing it. See the figure on the right for the inheritance pattern.

**Pathophysiology of HHT**

A defect in the TGF-B superfamily receptor results in an abnormal architecture of vessels with consequent malformations and aneurysms. This defect, 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

Clinical manifestations of the condition do not appear at birth; they 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 (> 90%). Varying in frequency and severity, it mostly develops till adolescence. In children, it is a strong indication of AVMs in the **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](image)

**Skin telangiectases** occur in > 75% of cases. Telangiectases are dilated blood vessels on the hands, **tongue**, face, lips, and **GI tract**. The **skin** lesions are often referred to as red spots. It is important to differentiate this characteristic manifestation from benign red spots.

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

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

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

**Iron deficiency/iron deficiency anemia** due to chronic blood loss is also common in HHT.

**Diagnosis of HHT**

The clinically driven diagnosis is based on the **Curacao 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 for 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 (a 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 an 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>
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<tr>
<td>Barium enema</td>
<td>Pulmonary AVMs</td>
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<tr>
<td>Contrast-enhanced MRI</td>
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<tr>
<td>Angiography</td>
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<td>Ultrasound and contrast radiography</td>
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<tr>
<td>Endoscopy</td>
<td>Reveal telangiectasis</td>
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<tr>
<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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<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 the 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-telangiectasis
- CREST syndrome
- Pediatric Syphilis
- Rosacea
- Rothmund-Thomson syndrome
- Scleroderma
- Cockayne syndrome
- Actinic keratosis

**Treatment of HHT**

HHT management 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
  - Tranexamic acid
- **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) (Comment: Recommendations vary from site to site, so better to delete)
  - Embolization
  - Liver transplantation
- **Long-term monitoring**
- **Newer Treatments/Anti-angiogenic therapies:** There is an increasing trend of the use of anti-VEGF therapies in patients with HHT. Thalidomide, Bevacizumab, and Pazopanib have reported some benefit.
Progression and Prognosis of HHT

Screening and appropriate management tend to increase overall life expectancy. HHT is associated with significant morbidity rather than mortality and the biggest factor affecting the quality of life is recurrent epistaxis in most patients. The prognosis depends on the disease severity and especially hepatic, pulmonary, and CNS involvement.

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