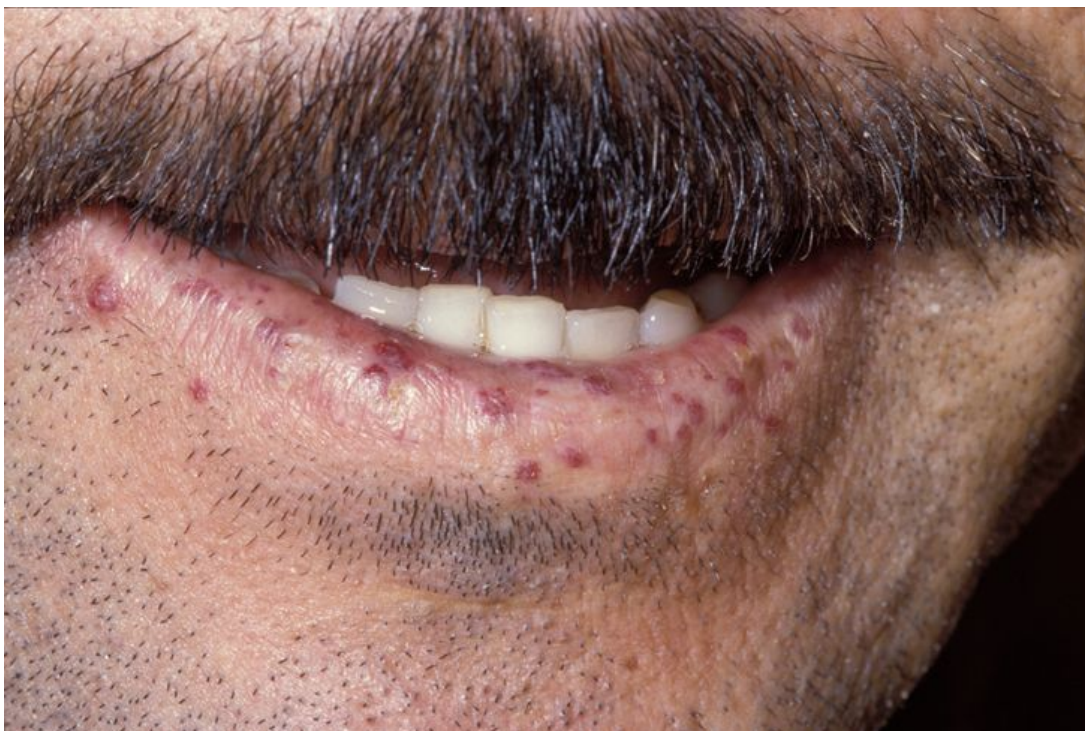


Hereditary Hemorrhagic Telangiectasia (HHT, Osler-Weber-Rendu disease) — Symptoms and Diagnosis

[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

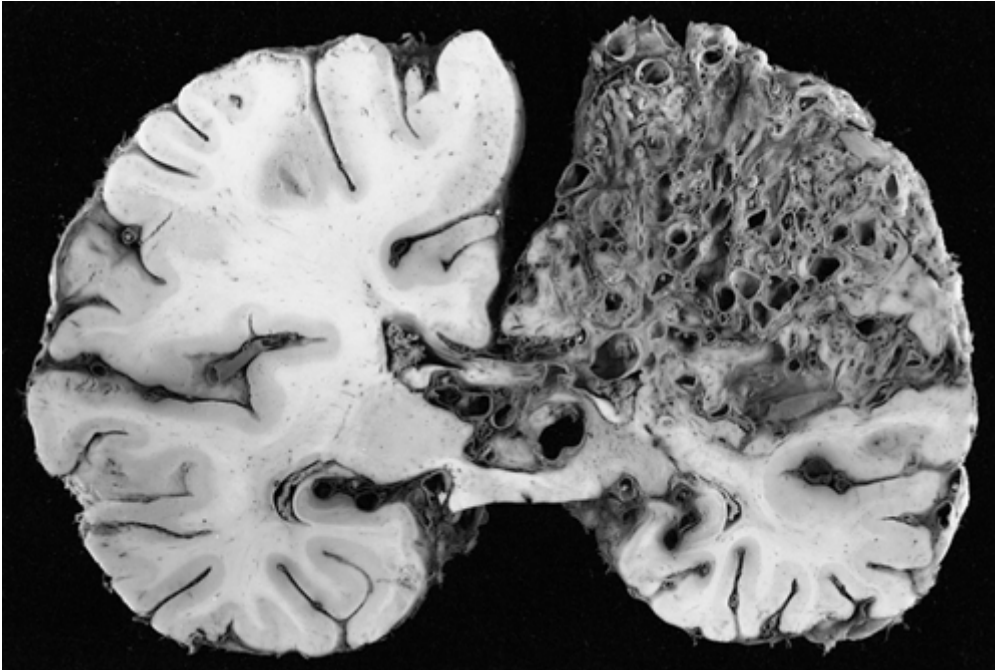
HHT as genetic disorder

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)

“Telangiectasia” and “arteriovenous malformation” both occur from a direct connection between an artery and a vein whilst 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, lung, and brain.



[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

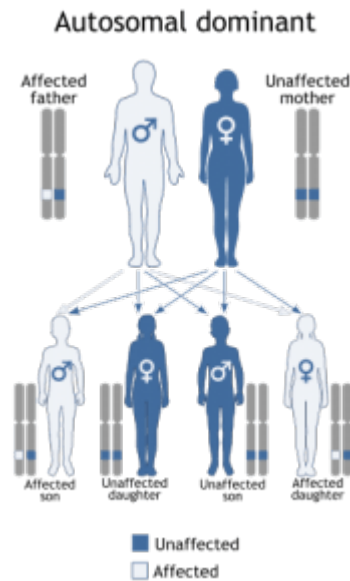


Image: "Autosomal dominant - genetics" by Domaina. License: [CC BY-SA 3.0](#)

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).

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 **Curacao criteria** and make use of the following 4 criteria:

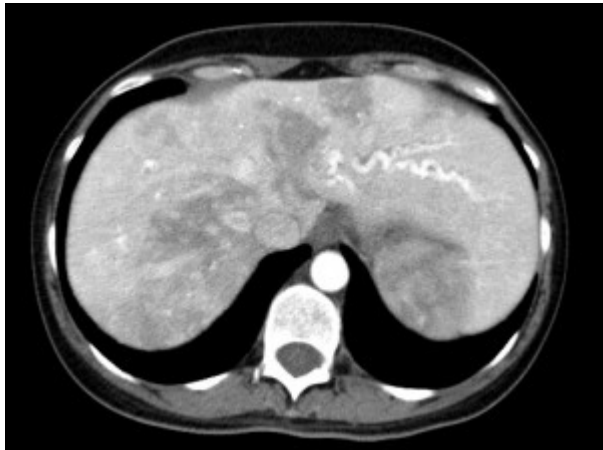
- Epistaxis
- Telangiectasis

- 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

Test	Significance
Chest radiography	May reveal enlarged mass of arteries and veins and/or peripheral non-calcified coin lesion
Transthoracic contrast echocardiography (TTCE)	Pulmonary AVMs
Barium enema	
Contrast enhanced MRI	
Angiography	
Ultrasound and contrast radiography	
Endoscopy	Reveal telangiectasis
Barium enema	Suspected ulcers and neoplasms
Helical CT	Delineating lung and brain AVMs
Abdominal CT	 <p><small>Image: "Axial computed tomography of the upper abdomen showing HHT" by Hellerhoff. License: CC BY-SA 3.0</small></p>

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

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
- 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 increasing trend of use of anti VEGF therapies in patients with HHT. Thalidomide, Bevacizumab, Pazopanib have reported some benefit.

Progression and Prognosis of HHT

Screening and appropriate management tend to increase the 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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Notes