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# Hereditary Hemorrhagic Telangiectasia – Osler-Weber-Rendu Syndrome: About A Case

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## Introduction

Hereditary Hemorrhagic Telangiectasia (HHT) is characterized by the presence of arteriovenous malformations (AVM), which lack capillary connections and result in direct junction between arteries and veins. Small AVMs are called telangiectasias. These telangiectasias are more evident on the lips, tongue, face, fingers, nasal, oral and gastrointestinal mucosa [1].

There are known three subtypes of the disease: HHT type 1, HHT type 2 and a combined form of Juvenile Polyposis Syndrome associated with HHT, depending on the genes involved. The estimated general prevalence is 1.5 to 2 cases per 10,000 people. In the United States, it presents in 1 of every 5,000 individuals. The highest prevalence has been reported in Afro-Caribbean regions, especially the Netherlands Antilles [2].

In light of clinical suspicion, family history, and presence of AVMs, diagnosis is made using the Curaçao criteria. However, it is estimated that only 10% of patients are diagnosed [3]. Treatment is symptomatic and preventive. We present a case of HHT with involvement of the nasal mucosa, gastrointestinal tract -iron deficiency anemia-, and lungs.

## Case Presentation

A 54-year-old woman with a history of hypertension and hypothyroidism, presented to the emergency department with a 3 months history consistent with asthenia, fatigue, intense headaches and melaena. Initial complete blood count showed a hemoglobin level of 6.9 g/dL without changes in other cellular lines. Complementary laboratories showed a profile compatible with iron deficiency (serum ferritin level 4.71 ng/mL, transferrin saturation 3.4%, serum total iron 14 µg/dL); normal serum electrolytes and kidney function. Appropriate initial management for upper gastrointestinal bleeding was started with a proton pump inhibitor (IPP), and a unit of red blood cells (RBCs) was transfused.

An upper gastrointestinal endoscopy was performed which resulted showing an atrophic gastritis, vascular angioectasia in antrum and gastric remnant without active bleeding (Figure 1). Mucocutaneous pallor and tongue telangiectasia where found on physical examination. Upon re-questioning the patient with the findings shown before, she described a history of recurrent epistaxis since a young age, and also in her mother and siblings, without previous medical consultations about it.

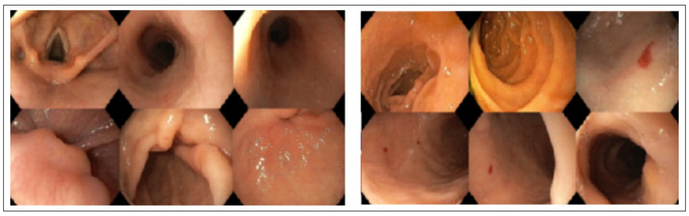

**Figure 1:** Esophagogastroduodenoscopy Pictures Showing Angioectasias in the Antrum and Gastric Remnant

In search of other arteriovenous malformations, a chest CT angiography was performed, showing tortuous pulmonary varices in the left and right lower lobes (Figure 2). A MRI of the brain showed a small area of acute infarction in the right frontal cortex (there was no neurological deficit on examination of the patient). An abdominal CT scan was also performed, showing small benign liver cystic lesions in segment IV and VI; transthoracic echocardiography was normal.

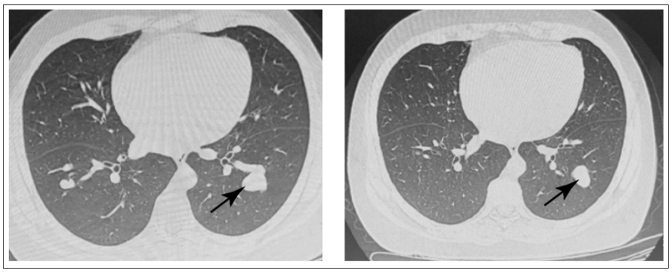

**Figure 2:** Chest CT angiography: Tortuous vascular structures described predominantly in the lower left lobe that communicate with the superior pulmonary veins, suggesting venous varices. The one on the left side seems to be in contact with a segmental branch of the left pulmonary artery, in the lower lobe; nonspecific; without ruling out arteriovenous fistula

A diagnosis of HHT was made by meeting 3 of the Curaçao diagnostic criteria: recurrent epistaxis, cutaneous telangiectasia and AVM in gastric mucosa and lungs. The patient had a good resolution of her symptoms, with no new bleeding episodes and a rising hemoglobin levels. Symptomatic management was provided and genetic studies were requested, with outpatient clinic control.

**Discussion**

HHT was initially described by Henry Gawen in 1864. In 1865 Benjamin Guy Babington reported the presence of epistaxis in five generations of a single family, and was differentiated from hemophilia for the first time in 1896 by Henri Jules Louis Marie Rendu. The eponymous was coined by William Osler, Henri Jules Louis Marie Rendu and Frederick Parkes Weber in the 19th century, who reported cases individually [4].

The hallmark of HHT is the angiodysplastic process that results in the formation of telangiectasias and AVMs throughout the body, predisposing to bleeding [5]. Telangiectasias occur on mucocutaneous surfaces, while AVMs occur on internal organs. Histological findings of AVMs are characterized by the presence of an irregular endothelium, increased collagen deposition and actin along with a contoured basement membrane [6].

It is an autosomal dominant disease with variable penetration. Several genes involved in the disease have been described. The first documented mutation was in the ENG gene on chromosome 9q34 which encodes for the Endoglin protein, a cell membrane glycoprotein in the beta growth receptor complex, responsible for cell signaling, angiogenesis and vascular remodeling, causing HHT type 1. The ACVRL1 gene, located on chromosome 12q13, encodes for activin receptor-like kinase 1 (ALK1), another cell membrane glycoprotein involved in the signaling pathway of growth factor beta with angiogenic properties, which, if mutated, causes HHT type 2. Finally, a mutation in the MADH4 gene, located on chromosome 18q21, results in a combination of Juvenile Polyposis Syndrome and HHT. The MADH4 gene encodes the SMAD4 protein, which is a signaling factor in the beta growth factor pathway [7].

Patients with HHT have abnormal levels of endothelial growth factor (VEGF) and growth factor beta (TGF-β). In up to 80% of the cases a genetic mutation can be found, being the ENG gene mutation the most frequent (61%), followed by the ACVRL1 gene (37%) and finally the MADH4 gene (2%). However, in 20% of the individuals with clinical criterial for HHT, mutations are not found [8].

These three mutations are involved in the signaling pathways of growth factor beta and bone morphogenic protein (TGF-β/BPM), having a significant role in cell growth, smooth muscle cell differentiation, apoptosis, remodeling and vascular maintenance [9].

There´s an estimated prevalence of the disease between 1:5,000 and 1:8,000 cases/individuals, with the highest in France, Denmark, Japan, and the Netherlands Antilles. There is also geographic variability depending on the subtype of the disease, being HHT type 1 more frequent in North America and Europe, while in South America and the Mediterranean the prevalence of HHT type 2 is higher [10].

The clinical manifestations are usually variable, ranging from mild cases of epistaxis, to severe visceral bleeding or massive AVMs with complications that can threaten life. The ENG gene mutations has been associated with AVMs in the lungs and brain; ACVRL1 gene mutations with hepatic AVMs, AVMs in the spinal cord, recurrent epistaxis and pulmonary hypertension; while MADH4 gene mutations has been associated with juvenile colonic polyposis [11].

Epistaxis is the most common manifestation. It occurs in up to 95% of cases, with an initial average-age of presentation of 10-years-old in 50% of patients [12]. Cutaneous telangiectasias occur around 90% of individuals, especially on fingers, hands, lips, tongue, and/or oral mucosa, and tend to bleed. They usually appear later in life [13]. About 20% of the cases present with gastrointestinal bleeding due to telangiectasias and AVMs in the stomach, small intestine and/or colon. Chronic anemia is associated with iron deficiency due to blood loss. AVMs in the central nervous system occur in 10% of the patients, with a varying range of manifestations: from asymptomatic patients, to those presenting with epilepsy, stroke, transient ischemic attack or spinal infarctions. Brain abscesses and strokes can occur after procedures such as dental prophylaxis, if bacteria bypass the pulmonary filtration system through a right-to-left shunt from AVMs in the lungs [14]. Around 70% of patients with HHT have AVMs in the liver, being the majority asymptomatic; however, the amount of blood bypassing through these AVMs can precipitate a high-output heart failure, liver failure, and/or portal hypertension. In 50% of patients, AVMs can be found in the lungs; up to 70% of all AVMs are due to HHT. Migraine is a frequent symptom and is presumed to be due to vascular pathophysiology at the brain [15].

Diagnosis for HHT is made using the Curaçao criteria (Table 1). The presence of 3 or more criteria confirms the diagnosis; HHT is considered possible with 2 criteria present, and less than 2 criteria will make it unlikely, ruling out the diagnosis. Genetic tests have been reserved to be used especially in cases of young patients, children who do not present typical symptoms, in the event of a diagnostic incongruency with the symptoms and as a screening method for prevention in first-degree relatives [16]. Since genetic behavior is variable, it is possible for identical mutations to develop in different individuals, showing different presentations. De novo mutations are rare and explain cases without family history [17].

**Table 1:** Curaçao Criteria: Presence of at Least 3 Criteria is Diagnostic. A Probable HHT is Suspected with the Presence of 2 Criteria. Less than 2 Criteria, makes the Diagnosis Unlikely

| Curaçao Criteria |
|---|
| 1. Spontaneous recurrent epistaxis. |
| 2. Multiple telangiectasias at characteristic sites (nose, oral cavity, lips, fingers). |
| 3. Visceral AVMs or telagiectasisas (brain, lungs, liver or gastrointestinal tract). |
| 4. A first-degree family history of HHT. |

Treatment is mainly for symptomatic support and eventual complications. There is no specific therapeutic approach. Among the therapeutic recommendations, an adequate education about screening methods should be carried out to the patient first-degree family members, in order to reduce possible future complications.

Iron deficiency anemia is one of the most frequent conditions found due to recurrent bleeding. Management consists of blood transfusions in severe cases. In mild to moderate cases, treatment with oral iron supplements is preferred [17]. Epistaxis, when moderate to severe, requires control with laser coagulation, sclerotherapy, electrocoagulation, embolization, or mucocutaneous grafts. In mild cases of epistaxis, control is achieved with local treatment based on nasal packing along with polyurethane, carboxymethylcellulose or latex tires. It should be taken in account that these procedures are not a definitive management since the development of new telangiectasias is likely. Regarding pharmacological management, the use of tranexamic acid is suggested as the first therapeutic option in mild cases, showing to improves hemostasis and increases ENG and ALK1 levels. It has been proven that the use of estrogens can generate squamous metaplasia of the nasal mucosa and improvement of vascular remodeling [17]. Otolaryngology follow-up should be guaranteed, and nasal care with saline washes is recommended, taking into account the recurrent formation of nasal crusts that can contribute to bleeding.

Central nervous system AVMS should be should be evaluated in conjunction with Neurosurgery. Both conservative and/or expectant management can be performed. Surgical or endovascular procedures are reserved for lesions greater than 1 cm. The recommended interventions are embolization, radiosurgery, stereotactic or multimodal therapies [17].

Pulmonary AVMs can cause serious complications such as septic or thrombotic embolisms, hypoxemia, and hemothorax with the risk of adverse outcomes. Among the recommended interventions are embolization via angiographic approach and occlusion with coils or vascular plugs. In case of fistulas, embolization is the main choice [17]. If superinfected lesions are suspected, antibiotic coverage should be prescribed prior to invasive procedures due to the risk of septic embolisms.

Regarding AVMs in the gastrointestinal tract, the best approach is through esophagogastroduodenoscopy, having the highest rates of successful outcomes. If bleeding persists, pharmacological management with antifibrinolytics and antiangiogenic drugs, such as Bevacizumab, should be considered [17]. For hepatic AVMs, a clear treatment hasn´t been defined given their complexity and risk of complications related to massive bleeding such as secondary hemoperitoneum. Angiographic embolization is not a recommended procedure for hepatic AVMs as it is associated with high mortality rates. In severe cases, liver transplantation may be considered [16]. Other therapies include Thalidomide, which has an immunomodulatory and vascular effect, decreasing the production of Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor (FGF). The use of Thalidomide in patients with gastrointestinal bleeding has shown a decreased VEGF levels, and mucosal biopsies in patients with epistaxis have demonstrated improvement in vascular walls and greater vascular maturation [18].

Bevacizumab, an anti-VEGF antibody, decreases angiogenesis and has shown favorable results in the management of epistaxis and gastrointestinal bleeding, controlling symptoms and reducing transfusion therapy requirements [19]. The dose ranges from 5 to 10 mg/kg of body weight every 2 to 4 weeks for 6 cycles on average. The most common adverse effects include high blood pressure, proteinuria, venous thromboembolism, and intestinal perforation. In a study including patients with hepatic AVMs, there was a significant improvement with in those treated with Bevacizumab using a dose of 5 mg/kg of body weight every 2 weeks for 6 cycles [20].

In general, the prognosis of HHT is favorable taking in account a timely diagnosis, use of supportive measures, and management of complications such as blood transfusions and iron supplements in those with iron deficiency anemia [16]. Without involvement of vital organs (brain, lungs o liver), the average life expectancy of a patient with HHT is similar to that of the general population. Mortality increases as complications such as brain abscesses, stroke, or severe bleeding appear.

Paradoxically, it has been shown that patients older than 60 years have a better prognosis than younger patients. However, there is an approximated 7% increase in thrombotic events in prostrated patients [17]. Pregnancy is considered a risk factor for worse outcomes, especially due to bleeding in the presence of pulmonary and brain AVMs.

## Conclusions

- HHT is a rare autosomal dominant inherited disease, and when present, clinical suspicion is usually low.
- The main clinical manifestations are recurrent epistaxis, cutaneous telangiectasias, chronic iron deficiency anemia and gastrointestinal bleeding.
- There are no differences in gender, it presents commonly in the third decade of life and more frequently in caucasian individuals, as well as in the described geographical regions.
- Diagnosis is usually clinical when it is suspected with the typical lesions applying the Curaçao criteria. This allows for a timely approach. Genetic testing is of little use in the clinical practice and is a complementary aid.
- Treatment is based on prevention, symptomatic relief and management of the possible complications.

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