Hereditary Hemorrhagic Telangiectasia - a literature review

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List of abbreviations
ACVRL1 = activin A receptor like type 1
AVM(s) = arteriovenous malformation(s)
CT = computed tomography
EGD = esophagastroduodenoscopy
ENG = endoglin
GI = gastrointestinal
HHT = hereditary hemorrhagic telangiectasia
HHT1 = hereditary hemorrhagic telangiectasia type 1
HHT2 = hereditary hemorrhagic telangiectasia type 2
JP-HHT = juvenile polyposis-hereditary hemorrhagic telangiectasia overlap
QoL = quality of life
SMAD4 = Mothers Against Decapentaplegic homolog 4
TGF-β = Transforming Growth Factor beta
TTCE = transthoracic contrast echocardiography
VEGF = vascular endothelial growth factor

Abstract
Introduction and purpose: Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a rare and complex vascular disorder characterized by abnormal blood vessel formation. It can present significant challenges in diagnosis and management, as it is currently estimated up to 90% of those affected are never diagnosed. Despite its rarity, HHT can carry substantial implications for patients and their families, at times requiring comprehensive medical care and support. This paper aims to provide an in-depth exploration of HHT, encompassing its epidemiology, genetics, clinical manifestations, diagnostic approaches, and current management strategies. Moreover, we hope to point out possible areas in need of future research.
**Description of the state knowledge**: HHT is an autosomal dominant genetic disorder that affects 1 in 5-10,000 people. Its most prominent symptoms include telangiectasia of skin and mucous membranes, recurrent epistaxis, gastrointestinal bleeding and arteriovenous malformations in vital organs. In the vast majority of cases, it is caused by a mutation in one of the following genes: ENG, ACVRL1, SMAD4; however, mutations in other genes have been described to cause a similar or much the same constellation of symptoms. Treatment options are focused on managing symptoms and improving quality of life, but possible new treatment options are being researched that could change the landscape of HHT management.

**Summary**: HHT is a severely underdiagnosed disease that has seen a surge of researchers’ interest in recent years. We firmly believe that, combined with plummeting costs of genetic testing and possible new treatment options, means that HHT will become increasingly important in physicians’ everyday practice.

**Keywords**: hereditary hemorrhagic telangiectasia, HHT, Rendu-Osler-Weber disease, Osler-Weber-Rendu syndrome, ORW disease, telangiectasia

**Introduction**

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a rare and complex vascular disorder characterized by abnormal blood vessel formation. It can present significant challenges in diagnosis and management, as it is believed that a vast majority of individuals with HHT are never diagnosed. Despite its rarity, HHT can carry substantial implications for patients and their families, at times requiring comprehensive medical care and support.

In this paper, we hope to summarize current knowledge about HHT and how it should be managed; we also hope to point out areas in need of further research. Second international guidelines for the diagnosis and management of hereditary hemorrhagic telangiectasia have been published in 2020; a number of research papers on the topic have been published since then, including research into additional genetic mutations and outcomes of newer forms of treatment.
State of knowledge

What is hereditary hemorrhagic telangiectasia?

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler disease or Rendu-Osler-Weber disease, is a rare autosomal dominant genetic disorder that leads to the formation of abnormal blood vessels in various tissues, most commonly skin and mucous membranes, but also in vital organs such as lungs, liver or brain [1]; therefore, symptoms can vary from harmless epistaxis to life-threatening cerebral hemorrhage [2]. As of now, there are no known means of preventing their formation; available treatment only targets symptoms. Additionally, the number of abnormal vessels naturally increases with age, which often leads to an increase in symptom intensity [3]. The exact pathophysiology of HHT is not known yet. However, the genes linked to HHT code for proteins in the TGF-β pathway [4,5,6,7,8,9,10] or related pathways [10,11]. Further research into the genetic basis of HHT may prove useful for developing more effective treatments and creating more reliable management guidelines.

The disease takes its eponym from Sir William Osler, who described it towards the end of the 19th century, and Henri Jules Louis Marie Rendu and Frederick Parkes Weber, who furthered the research into HHT in the early 20th century [12]. However, the biggest leap in our understanding of HHT came in the late 20th and early 21st century, when, among other factors, genetic testing has allowed contemporary researchers to establish some of the underlying causes of the disease; that leap is still happening to this day.

Epidemiology and genetics

While the exact prevalence of HHT varies across populations, it is estimated to affect approximately 1 in 5,000 to 1 in 10,000 individuals worldwide [1]. However, due to underdiagnosis and variability in symptom severity, the true prevalence might be higher; it is estimated that up to 90% of individuals with HHT are not diagnosed [2]. HHT exhibits variable expressivity, meaning symptoms can vary widely even among individuals within the same family carrying the gene mutation. Symptoms typically manifest during adulthood, although they can appear at any age [1].

The most commonly implicated genes are endoglin (ENG) [5], activin receptor-like kinase-1 (ACVRL1) [4], and Mothers against decapentaplegic homolog 4 (SMAD4) [6] (Table 1), all of which code for proteins partaking in the transforming growth factor beta (TGF-β) pathway.
Table 1. A summary of the most important HHT variants. Author’s own work.

<table>
<thead>
<tr>
<th>Variant name</th>
<th>Genes &amp; proteins affected</th>
<th>Proteins affected</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HHT variant 1</td>
<td>ENG</td>
<td>endoglin - an auxiliary receptor of TGF-β1 and TGF-β3</td>
<td></td>
</tr>
<tr>
<td>HHT variant 2</td>
<td>ACVRL1</td>
<td>activin receptor-like kinase 1 (ALK1) - a TGF-β1 receptor</td>
<td></td>
</tr>
<tr>
<td>HHT associated with juvenile polyposis (JP-HHT)</td>
<td>SMAD4</td>
<td>SMAD4 - an intracellular signaling protein for the TGF superfamily receptors</td>
<td>mutations in SMAD4 cause HHT and juvenile polyposis</td>
</tr>
</tbody>
</table>

In recent years, efforts have been made to ascertain whether testing for RASA1 and GDF2 should be considered in patients presenting with symptoms typical for HHT [10], especially in patients with suspected HHT, but with <3 Curacao criteria present. Mutations in both of these have been detected in patients presenting with symptoms characteristic for HHT who had previously tested negative for ENG, ACVRL1 and SMAD4 [10].

Aberrations in the first of those genes, RASA1, have been described to cause a variant of HHT [10,11]; they also cause other disorders affecting blood vessels, such as Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM syndrome), symptoms of which overlap significantly with those of HHT, which may lead to inaccurate diagnoses [11]. While proteins coded by RASA1 are not a direct part in TGF-β pathways, Ras pathways have been described as “co-operating” with TGF-β in regulating epithelial function [XYZ].

The second of these genes, GDF2, codes for bone morphogenetic protein 9 (BMP9), a ligand in the TGF-β signaling pathways. Mutations in this gene have also been described in patients presenting with symptoms typical for HHT in the few studies which as of now have examined the subject [7, 8, 9, 10].
### Diagnostic criteria and clinical characteristics

The diagnostic criteria for HHT, the Curacao criteria, were first established in the year 2000 [13] and upheld in both the International guidelines for the diagnosis and management of hereditary haemorrhagic telangiectasia 2009 [14] and Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia in 2020 [15]. These are shown below (Table 2):

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description of criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>spontaneous, recurrent nose bleeds</td>
</tr>
<tr>
<td>Telangiectases</td>
<td>multiple, at characteristic sites:</td>
</tr>
<tr>
<td></td>
<td>● lips</td>
</tr>
<tr>
<td></td>
<td>● oral cavity</td>
</tr>
<tr>
<td></td>
<td>● fingers</td>
</tr>
<tr>
<td></td>
<td>● nose</td>
</tr>
<tr>
<td>Visceral lesions</td>
<td>such as</td>
</tr>
<tr>
<td></td>
<td>● Gastrointestinal telangiectasia (with or without bleeding)</td>
</tr>
<tr>
<td></td>
<td>● Pulmonary AVM</td>
</tr>
<tr>
<td></td>
<td>● Hepatic AVM</td>
</tr>
<tr>
<td></td>
<td>● Cerebral AVMs</td>
</tr>
<tr>
<td></td>
<td>● Spinal AVM</td>
</tr>
<tr>
<td>Family history</td>
<td>a first degree relative with HHT according to these criteria</td>
</tr>
</tbody>
</table>

Table 2. The Curacao criteria [13].

The HHT diagnosis is considered to be:
- **definite** - if 3+ criteria are present,
- **possible/suspected** - if 2 criteria are present, and
- **unlikely** - if fewer than 2 criteria are present.

These criteria show high sensitivity: according to Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia, 97% of patients with a definite clinical diagnosis, a mutation in one of the 3 genes mentioned above is
Genetic testing can be used as a screening tool, as well as ruling out or confirming the diagnosis in patients suspected for HHT.

As useful as the Curacao criteria are, it is not always easy to make a definite diagnosis, as symptoms and their severity can vary significantly even among close relatives. However, they can be divided into two categories based on their etiology:

1. Skin and mucous membranes telangiectasia: small dilated blood vessels, particularly in the nose, lips, fingers and gastrointestinal tract.
   a. Recurrent epistaxis (nosebleeds) - as mucous membranes of the nose are frail, malformations are very likely to rupture there.
   b. Gastrointestinal bleeding
   c. Anemia - chronic bleeding can result in low red blood cell count, leading to fatigue and weakness.

2. Arteriovenous malformations (AVMs) - abnormal connections between arteries and veins, often affecting vital organs like the lungs, liver, and brain. While usually asymptomatic, they may lead to a wide range of complications, from mild to catastrophic in effect.
   a. Pulmonary AVMs (PAVMs) - they can allow blood to bypass the normal lung capillaries, leading to the possibility of unfiltered blood reaching the systemic circulation and causing, among others, strokes and brain abscesses.
   b. Hepatic AVMs - relatively rarely lead to complications including, among others, high-output heart failure and pulmonary hypertension.
   c. Cerebral AVMs - AVMs in the brain can pose a risk of hemorrhage, depending on their size and location. Regular monitoring and, in some cases, intervention may be necessary. They can hemorrhage abruptly or, rarely, produce signs of slow compression.
   d. Gastrointestinal AVMs - these may lead to gastrointestinal bleeding.

Management and treatment approaches

There does not exist any cure for HHT; thus, management of HHT consists of minimizing the impact of symptoms on patients’ quality of life and surveillance targeting possible complications.
Epistaxis

Depending on symptom severity and response to treatment, management can consist of the following [15], from least to most invasive (Figure 1):

- **moisturizing topical therapies** - humidification of the nasal mucosa reduces the risk of brittle vessels rupturing; e.g. topical saline twice daily.

- **oral tranexamic acid** - recommended in patients that did not respond to moisturizing topical therapies; treatment should start at 500 mg twice daily, gradually increasing as needed up to 1000 mg four times a day or 1500 mg three times a day.

- **ablative therapies for nasal telangiectasias** (laser treatment, radiofrequency ablation, electrosurgery, and sclerotherapy) - recommended in patients who did not respond to moisturizing topical therapies; their effect is rarely permanent, while requiring the risk of nasal septum perforation.

- **systemic antiangiogenic agents** - recommended in patients that did not respond to moisturizing topical therapies, oral tranexamic acid and/or ablative therapies; bevacizumab has been proven to reduce epistaxis, improve anemia, reduce transfusion requirements and improve quality of life; however, it requires monitoring and is contraindicated in pregnancy and before major surgeries. Risks of long-term therapy are not known.

- **septodermoplasty** - recommended in patients that did not respond to moisturizing topical therapies, ablative therapies, and/or tranexamic acid; it has been shown to reduce epistaxis, improve anemia, reduce surgical reintervention and improve QOL.

- **nasal closure surgery** - recommended in patients that did not respond to moisturizing topical therapies, ablative therapies, and/or tranexamic acid; has been shown to reduce epistaxis. While effective, the patient can no longer breathe through their nose, and smell and taste may be impaired.

In acute epistaxis, treatment should include packing with materials or products that are not likely to cause rupture when removed, e.g lubricated low-pressure pneumatic packing.
Figure 1. Recurrent epistaxis management recommendations, ordered from first to last line of treatment; any intervention should only be considered when one or more interventions above it have proven ineffective, and alternative treatments should always be considered. Author’s own work.

Multiple studies have been published in recent years evaluating the efficacy of intravenous bevacizumab; the vast majority of them confirm its usefulness in treating recurrent bleeding in HHT [16,17,18,19,20]. Two of the studies we could find evaluated the safety and efficacy of intranasal injections of bevacizumab, both of which showed short-term usefulness for this form of treatment [21,22]. Studies into long-term safety and efficacy are still lacking. Nasal administration of bevacizumab has been shown to be ineffective by 2 randomized studies [23, 24].

**Gastrointestinal bleeding**

In patients suspected of gastrointestinal (GI) bleeding, esophagastroduodenoscopy (EGD) is recommended as the first-line diagnostic tool [15]. In patients with a proven SMAD4 mutation and those who meet colorectal cancer screening criteria, both EGD and colonoscopy should be performed, as chronic GI bleeding is a hallmark symptom of colorectal cancer. In fact, patients with SMAD4-HHT should have a colonoscopy performed every 3 years starting at age 15 years, given the disease’s overlap with juvenile polyposis [15]. If EGD does not reveal telangiectasias that could explain the severity of anemia, capsule endoscopy should be considered, as it has been shown to be safe and effective [15, 25].
Endoscopic argon plasma coagulation in non-life threatening situations should be used sparingly as a way to protect intestinal mucosa from repeated injury, considering the recurrent character of GI bleeding in HHT, thus requiring multiple interventions over the course of the patient's life [15].

According to Second International Guidelines, HHT-related GI bleeding should be classified according to the patient’s individual hemoglobin goals, based on their age, gender, symptoms and comorbidities (Table 3).

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>patient who meets their hemoglobin goals with oral iron replacement</td>
</tr>
<tr>
<td>Moderate</td>
<td>patient who meets their hemoglobin goals with intravenous iron treatment</td>
</tr>
<tr>
<td>Severe</td>
<td>patient who does not meet their hemoglobin goals despite adequate iron replacement or requires blood transfusions</td>
</tr>
</tbody>
</table>

Table 3. HHT-related GI bleeding classification [15].

Mild HHT-related GI bleeding can be treated with oral antifibrinolytics, such as tranexamic acid. Cases of moderate and severe HHT-related GI bleeding can be treated with systemic antiangiogenic therapy, e.g. intravenous bevacizumab.

Anemia

All adults should be screened for iron-deficiency anemia, regardless of symptoms frequency or severity [15]. In case of iron-deficiency anemia, oral iron supplementation should be considered as an initial treatment; in some patients intravenous iron supplementation is necessary, namely when oral supplementation is not effective or not tolerated, or in severe anemia. It is important to consider other possible causes of anemia, especially when the response to iron supplementation is inadequate.

Patients with HHT should not be excluded from anticoagulation and antiplatelet therapy [15,26,27], however, they require monitoring. Unfractionated heparin, low-molecular-weight heparin, and vitamin K antagonists tend to be better tolerated than direct-acting oral anticoagulants. However, if possible, dual antiplatelet therapy and a combination
of antiplatelet and anticoagulant therapy should be avoided; if those are required, the duration of therapy should be minimized.

**AVMs**

The decision whether to attempt to treat AVMs or to continue surveillance is highly individual and depends on the location of the AVM in question, the patient’s symptoms and the expected prognosis after the treatment. Many of the possible interventions are very invasive in their nature, so their possible complications need to be balanced against possible AVM complications [28]. If possible, treatment should be managed at an HHT Center of Excellence [15]. Nevertheless, the most common locations, complications and management of AVMs in HHT have been summarized in Table 4.

<table>
<thead>
<tr>
<th>Location of AVM</th>
<th>Management</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>liver [29]</td>
<td>diuretics, liver transplantation</td>
<td>high-output cardiac failure, pulmonary hypertension</td>
</tr>
<tr>
<td>lungs [30]</td>
<td>embolization; antibiotic prophylaxis before surgical procedures</td>
<td>brain embolism, central nervous system infection</td>
</tr>
<tr>
<td>brain</td>
<td>surgery, gamma knife surgery, embolization</td>
<td>intracranial hemorrhage,</td>
</tr>
</tbody>
</table>

Table 4. Summary of most common locations, complications and management of AVMs in HHT. Author’s own work.

**Pregnancy & delivery**

Pregnancy in HHT presents unique considerations due to the increased risk of bleeding and complications associated with the condition. As the cardiovascular system adapts to the new conditions, women with HHT may experience exacerbation of symptoms such as recurrent nosebleeds and gastrointestinal bleeding during pregnancy, potentially leading to anemia and necessitating close monitoring and management. Additionally, the presence of AVMs, particularly in the lungs and brain, poses risks of complications such as hemorrhage or stroke during pregnancy and childbirth. Thus, women who have not been recently screened for pulmonary AVM should have agitated saline transthoracic contrast echocardiography (TTCE) or low-dose noncontrast chest computed tomography (CT) done, preferably early in the second trimester [15,31]. If the patient is presenting symptoms
suggesting a pulmonary AVM, CT should be performed at any gestational age [15,32]. In patients whose symptoms suggest a brain AVM, unenhanced MR is recommended as the diagnostic tool of choice. Careful planning and coordination between obstetricians, hematologists, and other specialists are essential to optimize maternal and fetal outcomes in pregnant women with HHT. Delivery planning should take into account the risk of bleeding and the presence of AVMs, with consideration given to the mode and timing of delivery to minimize the risk of complications; however, women with known, non–high-risk brain AVMs can labor and proceed with vaginal delivery. Moreover, withholding of the epidural is not recommended, nor is screening for spinal AVMs before delivery [15].

Quality of life and psychosocial aspects

While for most patients the disease is not life-threatening, the variance of symptom severity even within a single family means professionals cannot simply assume HHT has little impact on the patients’ quality of life. On the contrary, it can have a profound impact on the quality of life of affected individuals due to its chronic, yet unpredictable nature. Recurrent nosebleeds, a hallmark symptom of HHT, can disrupt daily activities, cause discomfort, and lead to anxiety about future bleeding episodes. Chronic anemia resulting from frequent bleeding can contribute to fatigue, further impairing quality of life. The presence of AVMs posing risk of life-threatening complications, especially those as widely recognized and feared as stroke or perinatal complications, adds to the psychological burden. The visible signs of HHT, such as telangiectasias on the skin and mucous membranes, may also affect the patients’ self-esteem and social interactions, leading to feelings of embarrassment or isolation. As mentioned above, the management of HHT often requires regular medical monitoring and sometimes interventions, such as embolization procedures or blood transfusions, all of which impact daily routines and contribute to emotional distress. Not to be underestimated is the fear of passing over the mutation to one’s offspring, considering the dominant nature of HHT’s heritability. Overall, addressing the multifaceted challenges posed by HHT is essential for optimizing the quality of life of patients, emphasizing comprehensive care that addresses both the physical and psychosocial aspects of the condition.
Challenges and Future Directions

There are a few areas of research that require further work; some more than others. While diagnostic tools have gotten cheaper and more accurate over the years, HHT is still massively underdiagnosed. It should not be surprising, considering how the severity of the symptoms varies and thus they can be limited to mild epistaxis, however, we doubt whether the 10-fold underdiagnosis can be explained solely by that. Mutations in genes other than ENG, ACVRL1 and SMAD4 require further research; in particular, mutations in RASA1 and GDF2 have shown some promise as possible causes of otherwise unexplained symptoms of HHT.

As of yet, there does not exist any treatment that would prevent the formation of new telangiectasias and AVMs. Existing treatments can alleviate the symptoms, but none are 100% effective and most of them can cause serious adverse effects. Of those existing treatments, new ways of drug administration require further research, namely intranasal injections of bevacizumab, as they show some promise in improving patients’ QoL in existing studies.

Summary

HHT is a rare vascular disorder characterized by abnormal blood vessel formation. Epidemiological studies estimate a prevalence ranging from 1 in 5,000 to 1 in 10,000, although it is estimated that up to 90% of individuals with HHT are never diagnosed.

HHT primarily results from mutations in genes encoding components of the TGF-β signaling pathway, including ENG, ACVRL1, and SMAD4. Mutations in other genes can produce a similar constellation of symptoms; the most well-studied so far are RASA1 and GDF2. Clinically, HHT manifests with a wide spectrum of symptoms, including recurrent epistaxis, gastrointestinal bleeding, anemia, and complications related to visceral AVMs, most commonly affecting the lungs, liver, and brain. The severity of these symptoms varies significantly even among close relatives. Clinical diagnosis of HHT relies on the Curacao criteria, which can be supplemented by genetic testing to confirm the presence of causative mutations.

Management of HHT focuses on symptom relief and prevention of complications, including topical therapies for epistaxis, iron supplementation for anemia, prophylactic testing for AVMs, and, in some cases, systemic pharmacological therapies or surgical interventions. Despite significant progress in understanding and managing HHT, several
challenges remain, including limited awareness among healthcare providers and the need for further research to fully understand the pathophysiology of HHT and develop targeted therapies. Some existing therapies may also be modified to better suit patients’ needs, e.g. administering bevacizumab intranasally instead of intravenously, which is the current standard. By advancing research efforts, we can improve the diagnosis, management, and outcomes for individuals living with HHT, ultimately enhancing their quality of life.

Authors’ contribution
Conceptualization, Marcel Stodolak; methodology, Marcel Stodolak, Piotr Sajdak; check, Mikołaj Turski, Aleksandra Krużel; formal analysis, Klaudia Żurowska; investigation, Artur Bednarski, Kamil Kłos; resources, Łukasz Szydłowski; data curation, Artur Bednarski, Justyna Tomasik; writing - rough preparation, Marcel Stodolak, Artur Bednarski, Piotr Sajdak; writing - review and editing, Justyna Tomasik, Marika Dębik; supervision, Seweryn Ziajor; project administration, Seweryn Ziajor; All authors have read and agreed with the published version of the manuscript.

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