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– ORIGINAL PAPERS –

Hereditary Hemorrhagic Telangiectasia - The Multiple Facets of A Rare Disorder

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Abstract

Introduction*: Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is a rare autosomal dominant disorder characterized by mucosal and cutaneous telangiectasia and systemic vascular malformations. HHT can be diagnosed using the Curaçao criteria. If at least three criteria are met, the diagnosis of HHT is considered definite.*

Purpose: *The objective of this study was to describe the clinical characteristics, management and complications of patients diagnosed with HHT and monitored in the Internal Medicine and Hematology Departments of the Fundeni Clinical Institute.*

Method: *A descriptive and retrospective study consisting of 24 patients over ten years (2014-2024).*

Results*: Out of 24 patients, 20 patients were women with a median age at the onset of symptoms of 28.3 years and at first admission in a clinical unit of 45.5 years. In 7 patients, genetic testing revealed mutations in the ACVRL1 and ENG genes. The most common reason for admission was nasal bleeding (91.6 %). The vascular malformations involved multiple visceral organs with the most common sites being the liver (50%), gastrointestinal tract (25%), lung (12.5%), pancreas (8.3%).. The management of the patients included blood transfusions, iron supply, argon plasma coagulation, radiological embolisation and liver transplantation. The main complications were due to upper gastrointestinal bleeding, heart failure and thrombosis.*

Conclusions*: HHT is an extremely heterogenous disease. Subjects from the same family often present with different sites of vascular malformations. At the moment, only symptomatic options of treatment are available in referral centers in our country. Angiogenesis inhibitors are considered prospective therapeutic options that have shown promising results in various studies. Early identification and treatment of symptoms and complications are crucial for enhancing the quality of life for individuals with HHT.*

Keywords*- hereditary hemorrhagic telangectasia, genetic profile,clinical presentation, multidisciplinary approach*

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Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is an autosomal dominant disorder characterized by the presence of mucosal and skin vascular ectasias and arteriovenous malformations (AVMs) in viscera such as brain, lung, gastrointestinal tract and uterus. Because of the heterogeneity of clinical manifestations, HHT is often misdiagnosed in the general population. The majority of HHT patients exhibit haploinsufficiency of genes involved in the signaling pathway of transforming growth factor B (TGF-B). The most common genetic abnormalities are in the activin receptor-like kinase 1 (ACVRL1) and endoglin (ENG) coding genes. ENG-1 mutations account for 61% of HHT cases and are labeled as the cause of HHT-1. ACVRL1 mutations are found in approximately 37% of patients and are labelled as HHT2. (1,2) About 5-10% of patients that meet the criteria for HHT don't have a germline pathogenic mutation in those two genes.(3) Mutated variants of SMAD4, RASA1 and GDF2 have also been described in individuals diagnosed with HHT. (4) SMAD-4 is also usually associated with juvenile polyposis-like HHT. (2,4) In rare cases, there is an overlap between HHT and other capillary malformations syndromes caused by mutations in EPBH4. (4) Active angiogenesis also plays a role in the development of vascular abnormalities. The spectrum of clinical manifestations ranges from recurrent nose bleeding, gastrointestinal and genital bleedings, congestive heart failure, liver failure and ischemic cerebral events. Pulmonary AVMs can also be the cause of cerebral abscesses or strokes. The Curacao criteria (consisting of family history, recurrent bleeding, presence of telangiectasia and visceral AVMs) and genetic testing are the most helpful tools in diagnosing HHT. The Curacao criteria are illustrated in Table 1

Criterion	Description	Examples / Notes
1. Epistaxis	Spontaneous and recurrent nosebleeds	Variable severity and frequency; might be first symptom
2. Telangiectasias	Multiple small red spots on characteristic sites	Lips, oral cavity, fingers, nose; blanch with pressure
3. Visceral Lesions	Arteriovenous malformations (AVMs) in internal organs	Lungs (PAVMs), brain (CAVMs), liver (HAVMs), GI tract (bleeding)
4. Family History	First-degree relative with HHT (by these criteria)	Suggests autosomal dominant inheritance

Table 1. *The Curacao Criteria used for screening of HHT; Diagnosis of definite HHT requires>=3 criteria to be met; 2 criteria indicate possible or likely HHT while <2 criteria is interpreted as unlikely HHT*

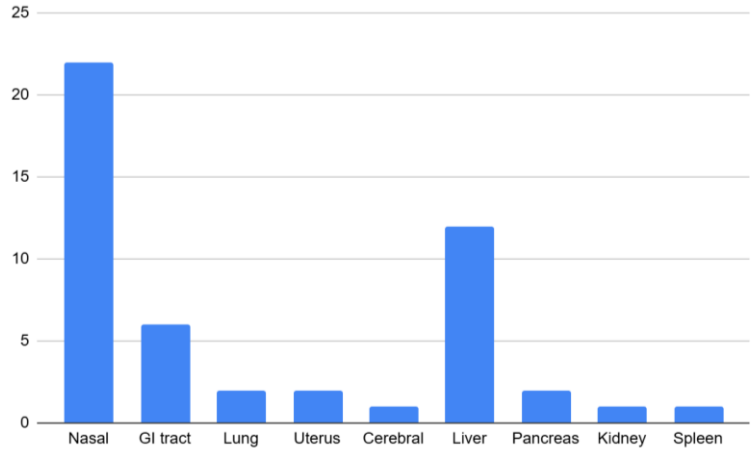

Figure 1-*Distribution of AVM sites; as stated in literature, the nasal and GI tract telangiectasias are the most common presentations of HHT.*

GI-gastrointestinal;

Treatment is primarily supportive and highly dependent on the AVM sites, ranging from conservative and interventional techniques to solid organ transplantation, for example lung and liver. Treatment often requires the management of a multidisciplinary team. Angiogenesis inhibitors such as Bevacizumab have proved their efficacy in the management of recurrent nasal and gastrointestinal bleeding.

Material and methods

This was a single-center, descriptive, retrospective study conducted over a 10-year period (2014–2024) in the Departments of Hematology and Internal Medicine at Fundeni Clinical Institute in Bucharest, Romania.

Data were collected from the hospital's electronic medical records. Inclusion criteria were:

1. At least two documented hospital admissions, and
2. A diagnosis of HHT based on the Curaçao criteria, with patients classified as having *definite HHT* (≥3 criteria met) or *possible HHT* (2 criteria met).

Collected variables included:

- Demographic data: age, gender, age at symptom onset, and age at diagnosis
- Clinical features: bleeding sites, presence and location of AVMs (confirmed via imaging or endoscopy), complications (e.g., heart failure, thrombosis, infection)
- Treatment history: use of conservative measures (iron supplementation, blood transfusions), interventional procedures (argon plasma coagulation, embolization), and surgical interventions (e.g., liver transplant)
- Genetic testing: when available, results for mutations in ENG and ACVRL1

Functional and imaging studies used to confirm AVMs included upper and lower endoscopies, abdominal ultrasound, CT and angio-CT scans, MRI, and echocardiography.

Statistical analysis was conducted using Microsoft Excel and IBM SPSS. Descriptive statistics were used to summarize the cohort's clinical and epidemiological features.

Results

The study group included 24 patients; 17 patients (70.83%) met the Curacao criteria for definite HHT., while the remaining 7 patients (21.66%) met the criteria for possible HHT. The eligible patients consisted of 20 females and 4 males, resulting in a female to male gender ratio of 5:1. The demographic profile of the study group is characterized by a median age at diagnosis of 43.1 years (range 35-67). The median age of symptom onset is 28.3 years (range 18-44). According to various meta-analysis studies about demographical data of HHT patients, the difference between the patient's age at diagnosis and onset of symptoms is explained by the fact that HHT is often misdiagnosed as other hemorrhagic diathesis such a hemophilia or von Willebrand disorder. (11)

All patients had a family history of at least one relative having documented episodes of recurrent bleedings. Three families have been included in this study; one consisting of a mother and a daughter, another family consisted of two identical twin sisters and their brother and the third one being made up of two brothers.

The most frequent bleeding sites sites were – nose(22 cases), gastro-intestinal tract (6 cases) and uterus (3 cases).

In order to screen for the presence of internal organs AVMs, various functional and imagistic investigations have been performed (fibroscopies, endoscopies, ultrasounds, CT and angioCT scans, MRIs). The results showed that the most common sites for AVMs were the nose septum (91.66%); followed by the liver (50%), gastro-intestinal tract (25%), lungs (8.33%) and brain (4.17%). Some rare AVMs sites (7) such as pancreas (8.33%); spleen (4.17%); kidney (4.17%) and spine (4.17%) have also been documented.

Because nose bleedings represent the most common symptom/sign in HHT the Epistaxis Severity Score (ESS) was established in order to guide proper management (6). The most common therapeutic measures recommended for severe nose bleeding include topical therapies, cauterisation, systemic agents such as tranexamic acid. (5,6) Out of the 21 patients, 18 presented with mild epistaxis that required nasal topics and local moisturizers. 2 patients presented a moderated ESS score, thus being candidates for ablative therapies. Septodermoplasty was not performed in any case.

According to the ASH guidelines, screening for pulmonary AVMs should include contrast echocardiography ("bubble echo"typical aspect).

Due to the fact that all patients presented with iron deficiency anemia, blood transfusions and iron supply represented the main lines of supportive treatment. (6.8) The current guidelines of the American Society of Hematology for managing anemia in HHT recommend oral iron therapy as first line treatment, with intravenous iron being second line. Blood transfusions are

recommended for patients that present with hemodynamic instability, comorbidities that require a higher hemoglobin level and inability to maintain proper levels despite frequent iron infusions (6.8). All 24 patients received blood transfusions at some point. The median value of hemoglobin at which blood transfusions were recommended was 6.7 g/dl (range 3-7.7 g/dl). On average, patients received a median of 7 units of red blood cells per year (range 1-30 units per year).

Interventional management of the AVMs found in HHT often proves challenging. The International HHT Guidelines recommend esogastroduodenoscopy as a first-line test in patients that are suspect for HHT-related bleeding (6,9). Endoscopic argon plasma and vessel embolization should be only used in active bleeding cases and on a limited number (10) of significant non-bleeding lesions (from 1to3 mm width) (6,9). Since there is no clear correlation between the number, size or distribution of the gastrointestinal vascular abnormalities and the severity of bleeding, the grading of symptoms is based solely on the severity of anemia and its impact on the hemodynamic status of the patient. (6) In our group, esogastroduodenoscopy was performed in 14 patients that either presented with active gastrointestinal bleeding or had documented AVMs. Out of the 12 patients that had documented AVMs of the viscera (liver, pancreas, spleen) 2 patients underwent hepatic vessel embolizations. One patient underwent the embolization of the splenic artery and other 3 patients underwent gastric coagulation with plasma argon for repeated episodes of upper GI bleeding. Out of the 12 patients that presented with hepatic AVMs, 3 were enlisted in the Romanian National Registry for liver transplant receptors because of the subsequent liver failure. One patient who also tested positive for the ENG mutation has already received a liver transplant in 2022.

Complications that appeared during the follow-up period have been the result of the hemodynamic impact of repeated blood transfusions and the presence of visceral AVMs. 7 patients (29.16%) have been diagnosed with heart failure, 5 patients (20.83%) were diagnosed with pulmonary hypertension, 2 patients (8.33%) developed atrial fibrillation and one patient (4.27%) had a splenic artery aneurysm that required surgical treatment. 2 patients (8.33%) also have been diagnosed with dilated cardiomyopathy. There were 2 cases (8.33%) of sepsis-one patient had a case of sepsis with Staphylococcus aureus with cutaneous and osteoarthritic involvement. The other patient had a case of multi-drug ressitant Klebsiella pneumoniae. 3 patients (12.5%) developed thrombosis (2 cases of lower-limb thrombosis, 1 case of portal vein thrombosis). In this case, the ASH Guidelines specify that anticoagulation therapy is indicated in HHT patients, with warfarin and heparin-based anticoagulants being preferred over DOACs, the main reason being the insufficient data in specialied literature (6, 10). One patient has been diagnosed with myelodysplastic syndrome /acute myeloid leukemia after 13 years of being diagnosed with HHT and receiving blood trasfusions for reccurent epistaxis. The patient refused to undergo chemotheraphy and only received conservative treatment. There was no post-transfusional hemochromatosis case detected.

Out of the 24 patients, 7 benefitted from genetic testing.The results showed that 4 patients were positive for the ACVRL-1 mutation while the other 3 tested positive for ENG-1.

One family (brother and two identical twin sisters) tested positive for the ACVRL-1 mutations. All family members presented with lung AVMs and subsequent pulmonary hypertension. The two sisters had a history of hydrocephaly during childhood; in addition, the two sisters also have hepatic AVMs with one of them being included in the Romanian National Registry for liver receptors. ACVRL-1 encodes the activin receptor-like kinase type 1 (ALK1) which is located on chromosome 12q. (12) It is a TGF-β superfamily receptor expressed on endothelial cells and plays a critical role in blood vessel formation and remodeling.(12) The brother presented with nasal and pulmonary AVMs; he also has a history of pulmonary hypertension and a portal vein thrombosis

The fourth patient that tested positive for the ACVRL-1 mutation doesn't have any other family members included in the study lot. According to recorded data, multiple family members from his maternal side presented recurrent epistaxis. His two sons have also been screened and they also tested positive for the ACVRL-1 mutation but they are asymptomatic at the moment. Multiple CT and angioCt scans showed multiple liver vascular shunts, a shunt between the spleen and the left kidney with no hemodynamic impact and very discrete vascular malformations in the left lingula. The patient also has two complication due to the multiple AVMs and blood transfusions-pulmonary hypertension and cardiac failure stage II NYHA.

The other family that benefited from genetic testing consisted of a mother and daughter. Both presented with recurrent epistaxis and hepatic AVMs. The mother was the sole receiver of an orthotopic liver transplant from this

study lot. Both females tested positive for the ENG-1 mutation which is found on chromosome 9q33-34 and encodes a membrane glycoprotein which modulates the response to TGF-B (13). Even though the data from the literature shows ENG-1 positive patients have a higher incidence of pulmonary and cerebral AVMs, the two females presented only with liver and nasal vascular abnormalities. The daughter also has a son that tested positive for the ENG-1 mutation but is currently asymptomatic.

The third patient that tested positive for ENG-1 is a female that presented only with nasal bleeding. There is a documented family history of epistaxis on her father's side. Her two sons also tested positive for the same mutation. One of them was also diagnosed with ADHD and died at 14 years old due to a severe case of pulmonary hypertension. The other son is asymptomatic at the moment.

Discussions

The above findings highlight the challenges in managing patients diagnosed with HHT and underscore the critical need of a thorough screening of possible arterio-venous malformations. In order to optimize treatment strategies diagnosis, tools such as imaging and functional investigations are required..

Genetic tests are not routinely available in our country, so only 6 out of 24 patients included in the study lot benefited from them.

Angiogenesis inhibitors such as Bevacizumab, Pomalidomide, Pazopanib are not yet registered in Romania for HHT patients. Recent studies show a benefit in the management of HHT patients that present with multiple AVMs sites.

Patients often present with more than one vascular abnormality. In our study, the most common association was between liver and nasal malformations.

The visceral AVMs represent the main cause of morbidity in individuals with HHT. 4 out of the 24 patients have died due to an acute episode of upper GI tract bleeding or complications of severe heart failure. One patient evolved to acute myeloid leukemia (AML), after myelodysplastic syndrome. Even though patients with HHT can present with pancytopenia due to hypersplenism, currently there are no cases in literature that attest the link between HHT and AML.

In our study, the most stringent characteristic was a significant difference between the age of symptoms'onset and the age at confirmed diagnosis (mean of 17.2 years). Awareness of pediatricians and general practitioners about clinical aspects in HHT could be the key to an earlier diagnosis. A cornerstone for management of HHT patients is national multidisciplinary guidelines development. Another issue worth considering should the prophylaxis of infections in HHT patients before certain invasive procedures (for example upper GI tract explorations or dental interventions).

There is also a real need for developing a national registry of HHT patients and their families. The most recent GRADE Guidelines recommend testing all children of individuals with Rendu-Osler-Weber syndrome, even if they are asymptomatic. (14)

Patient	Gender	Family history	AVM site	Complications
1	F	unknown	Nasal, uterus, GI tract	Cardiac failure and subsequent pulmonary hypertension, infectious
2	F	unknown	Nasal	Massive epistaxis requiring frequent blood transfusions
3	F	Father, paternal aunt	Nasal, uterus	No
4	M	Brother	Nasal	No
5	M	Brother	Nasal	Acute myeloid leukemia post myelodysplastic syndrome
6	F	unknown	GI tract (duodenum), uterus	Cardiac failure NYHA II, Atrial fibrillation, repeated argon plasma procedures

7	F	unknown	Nasal, GI tract	No
8	F	Mother, daughter	Nasal, liver,	No
9	F	Father, 2 sons -ENG1 positive	Nasal	No
10	F	Paternal side-grandparents, aunt, daughter	Nasal, liver, pancreas	No
11	F	Brother, sister. mother-ACVRL1 positive	Nasal, liver	Listed in the national liver transplant registry, GI bleeding history
12	F	Brother, sister, mother-ACVRL1 positive	Nasal, liver	Listed in the national liver transplant registry, GI bleeding history
13	M	Mother, 2 sisters-ACVRL1 positive	Nasal, lungs	Pulmonary hypertension, portal vein thrombosis
14	M	Brother, mother, 2 sons-ACVRL1 positive	Nasal, lungs, spine	Pulmonary hypertension, cardiac failure NYHA II
15	F	Mother, 2 sisters	Nasal, GI tract, liver	Multiple GI bleeding episodes, cardiac failure NYHA II, A fib, pulmonary hypertension
16	F	Mother; ENG-1 positive	Nasal, liver, cerebral	Cardiac failure HYNA II-III; pontine demyelination; lower limb thrombosis
17	f	Father	Nasal, kidney, liver	Cardiac failure
18	F	unknown	Nasal	No
19	F	Mother, brother, aunts (maternal side)	Nasal, liver, spleen	Cardiac failure, pulmonary hypertension, splenic artery aneurysm that required embolisation
20	F	unknown	Nasal, liver, pancreas	Liver cirrhosis and GI bleeding
21	F	unknown	Nasal, duodenum, liver	Mesenteric vein thrombosis
22	F	Mother; tested ENG-1 positive	Nasal, liver	Orthotopic liver transplant recipient
23	F	Maternal side	Nasal	
24	F	Maternal side	Liver, GI tract	Multiple GI bleeding episodes

Table 2. *Detailed breakdown of the gender, family history and AVM sites of the 24 patients included in this study.*

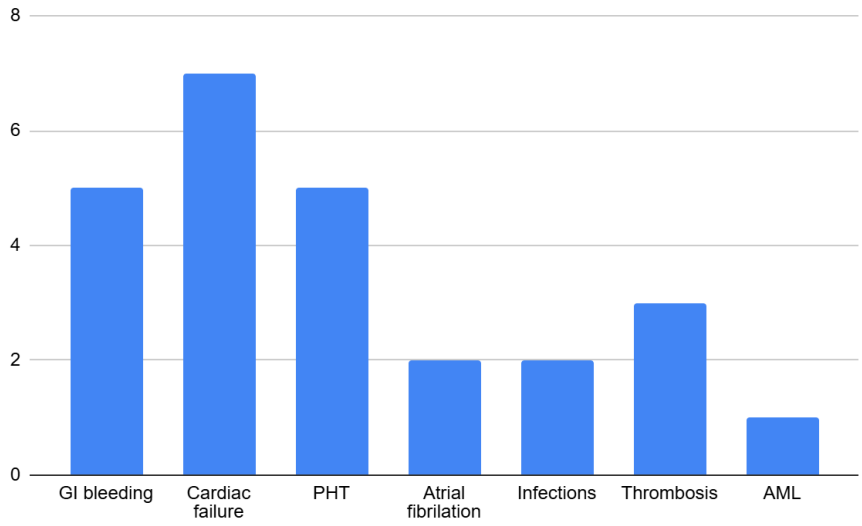

Figure 2*-distributions of complications in HHT patients; the main cause of complications is represented by the hemodynamic impact of the numerous bleeding episodes;*
AML-acute myeloid leukemia; GI-gastrointestinal; PHT-pulmonary hypertension

Conclusion

The findings of this real-world study are similar with those reported in clinical studies focused on the diagnosis and management of individuals with HHT. (14)

A multidisciplinary team consisting of hematologist, internist, gastroenterologist, radiologist and ENT specialist are often the key to a proper and successful management of HHT. The future of HHT research should focus on periodically screening for the presence of recently acquired AVMs. Genetic tests for suspected cases and already diagnosed patients and their family members are recommended. Both germline and somatic mutations have been shown to be involved in the development of overt HHT. (1,2)

Ethics Statement and Conflict of Interest Disclosures

Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

Ethics Consideration: The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by all participants in this study.

This study was approved by the Institutional Research Board and Ethics Committee.

Conflict of interest: No known conflict of interest correlated with this publication.

Availability of data and materials: The data used and/ or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interests: The authors declared that they have no competing interests.

The use of generative AI and AI-assisted technologies: The authors did not use in this article generative AI and AI-assisted technologies.

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