European Reference Network
for rare or low prevalence complex diseases

Network Vascular Diseases (VASCERN)

Report on the Based on Evidence European Meeting

25th May, 2023, Taastrup, Denmark

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Introduction

The Based on Evidence European (BEE) Meeting is a bi-annual two-day educational symposium gathering HHT experts, clinicians, healthcare professionals, and patients/caregivers from across Europe. It was established to foster collaboration, innovation, and the dissemination of knowledge on cutting-edge research and treatments in HHT.

The first edition of the symposium took place in Taastrup, Denmark on 25th May, 2023 with topics presented by 14 experts and more than 60 participants at the meeting. The topics ranged from diagnostic criteria and genetics to the daily challenges faced by HHT patients. The symposium provided a platform for interdisciplinary approaches and knowledge exchange, fostering a collaborative environment that aimed to deepen the understanding of HHT.

Throughout the event, participants engaged actively, contributing to discussions and forming connections that will undoubtedly propel collective efforts in understanding and managing HHT. The symposium served as a nexus for professionals and patient advocates dedicated to enhancing the quality of life for individuals affected by HHT.

This document summarizes the presentation on the topics at the first edition of the BEE meeting. The BEE meeting is planned to be held every second year, in Europe, in order to keep the knowledge updated and to educate more doctors within the field of HHT

We extend our gratitude to all participants who made this symposium a success, contributing to the exploration and advancement of knowledge in the realm of rare vascular diseases.

Diagnostic Criteria

Prof. Anette Kjeldsen

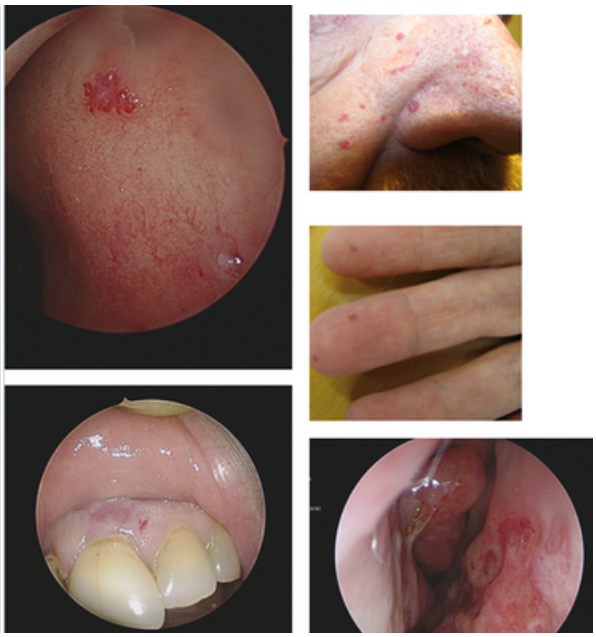
The clinical diagnostic criteria for HHT were reviewed. Mutation diagnostics are not included in these clinical criteria. In families with a known family mutation, the HHT diagnosis can be confirmed or ruled out for first-degree relatives.

The presence of telangiectatic lesions is part of the Curacao Criteria (2000) (1), though at that time, an exact description of the appearance of the lesions was lacking. Several publications have focused on the distribution and morphology of these lesions (2). There is a general agreement that the number of lesions increases with age (3). The telangiectatic lesions typically occur in the locations mentioned in the Curacao Clinical diagnostic Criteria of HHT: fingers, nose, oral mucosa, skin of the face, and lips.

Telangiectatic lesions can exhibit various appearances. The classic well-known lesions are round, elevated, or flat and can become tortuous or confluent. The color may vary, appearing pinkish or blue. Their morphology and number may differ between HHT subtypes, but not in a way that allows the clinician to differentiate between the different HHT subtypes (4).

HHT patients also have elongated linear lesions. Although the linear lesions were discussed as potentially characteristic of HHT, they cannot be considered part of the diagnostic criteria at this point.

Examples of telangiectatic lesions are shown in the figure.



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Genetics in HHT

Dr. Pernille Tørring

HHT follows an autosomal dominant inheritance pattern with significant intra-familial variability and age-dependent penetrance. This genetic disorder is due to pathogenic variants primarily in ENG or ACVRL1, while SMAD4 variants are rare (occurring in around 3% of cases) and lead to HHT combined with juvenile polyposis. In a smaller fraction of HHT families, the pathogenic gene variant remains unidentified. Genetic testing for HHT is recommended to encompass relevant differential diagnoses (RASA1, EPHB4, GDF2/BMP9) in addition to ENG, ACVRL1, and SMAD4.

Prenatal and preimplantation genetic testing are possible if the pathogenic variant is known in the family, although it is seldom requested by HHT patients (especially in ENG and ACVRL1 families). Decisions regarding prenatal genetic testing rest with the parents, but thorough discussion of all related issues is advisable.

The two-hit hypothesis has been widely accepted for many years as a plausible explanation for the observed phenotypic variability in HHT. The germline heterozygous pathogenic variant (first hit) result in monoallelic protein loss in endothelial cells. The second hit is thought to be either an environmental stimulus (such as inflammation, hypoxia, vascular injury, or trauma) or a local genetic variant on the normal HHT allele (of the same gene), or possibly a combination of both. In all cases, the consequence is impaired endothelial cell function, leading to the development of telangiectases and AVMs. Current clinical data, as well as in vivo and in vitro experimental results, support the second-hit hypothesis as an explanation for the incomplete penetrance and significant clinical variation observed in HHT. Nevertheless, substantial gaps in our knowledge persist.

Living with HHT from the HHT patients perspective

Tove Østergaard

My name is Tove Østergaard and I am the chairman and co-founder of the Danish patient organization Osler/HHT Denmark. First of all, my co-chair June Hartmann and I would like to thank you for the invitation to be here today, we are looking forward to enjoying the day with all your good and clever doctors from all over Europe.

Tove Østergaard and her father pictured

I inherited the disease from my father, as did my only sister. My only daughter luckily did not inherit the disease 😊. The accompanying photo is of my dear father and me at the OUH in 1981. He had just had an operation to add skin from his thigh up to his nose. I have several perspectives on living with HHT, but today, due to lack of time, I will only talk about how I deal with my HHT in good and bad ways.

Firstly, I would like to tell you where my HHT affects me in and on my body. I have a lot of nosebleeds, HHT elements on my tongue and lips, and elements in my liver and stomach. My hands and fingers are also affected. As for the nosebleeds, I feel it is a human right to do the following: blow my nose, sneeze, yawn, cough, cry, and laugh. As an HHT patient, you CANNOT do any of these things without bleeding, or you have to be very careful. But of course, I can only speak for myself.

Before I leave home, I always take a bag with me that contains lots of handkerchiefs, absorbent cotton wool, ice cubes in a small thermos flask, salt water, which I use a lot of, a small mirror, pills called Cyklonova and liquid called Lidokain. Sometimes I take Rapid Rhinoes with me. That is quite a lot to remember and carry around. You need to understand that it is a very, very heavy backpack to carry around physically and mentally.

I have had laser surgery on my nose several times, but unfortunately, it does not work for me. That is why I have managed with the tablets called Cyklocapron, and the liquid called Lidokain on absorbent cotton wool that I put up in my nose. I also use a lot of ice cubes that I put in my palate and on my nose. With a lot of help from my husband, we have managed to stop the bleeding most of the time. I have also had laser surgery on my stomach and it has worked. In connection with this, I stopped taking iron tablets about 6 years ago and now have iron transfusions (monofer) and have had very little stomach bleeding since. The HHT in my liver does not yet require treatment.

I would like to point out to you that many HHT patients have mental anxiety about unexpected nosebleeds, people always get upset when they see blood, and I know this from talking to members of our patient association. I am always a bit nervous about going to the dentist, the cinema, the theatre, going to a party with people I do not know, giving a speech (but not here as you all know about blood and bleeding, I presume), having an appointment at a specific time (e.g. if I have to catch a flight), having an important meeting, and so on, I could go on indefinitely.

Lastly, I wonder how HHT can rest for a while (without treatment) and then come back later with renewed strength. I hope one day you doctors will find out what is going on 🙏.
Thanks for listening 😊. If you have any questions, I will try to answer them

June Hartmann

My name is June, and I am 46 years old. I have HHT and have known about it all my life. My dad has HHT, and my grandmother and aunt had HHT.

June Hartmann and her family pictured

The accompanying image shows three generations of my family with HHT. The woman on the left is my grandmother. She was hospitalised a week before I was born because of severe blood loss due to HHT. She was never discharged. My grandfather visited her in the hospital every day. The picture was taken on one of her leaves from the hospital, which almost always ended with her in an ambulance on her way back to the hospital. She died in hospital in 1993 at the age of 72 years, and 18 years after being admitted. She had severe nosebleeds and intestinal bleeding, and she had blood transfusions almost every day. She had practically no stomach left because it was surgically removed in bits to stop the bleeding. She died of an infection in her portacath.

The handsome man on the top left is my dad. He will be 72 this year and has had severe nosebleeds since he was in his 30s. In his early 60s, his nosebleeds were so severe that he almost gave up on life. He had many blood and iron transfusions, but his quality of life was very poor. He did not want to leave the house, not even to visit his family for birthdays, for fear of not being able to stop the nosebleeds. Then he had the Young's procedure in 2013 and his life turned around. His quality of life came back, he started getting out of the house every day and was much happier again. I got my dad back!

But HHT has a way of finding new places to bleed, so his intestines started to bleed. It was the same situation again. He stopped going out, he just lay on the sofa and had given up on life. Bevacizumab saved his life and for the last 7 years, he has had his quality of life back.

Why am I telling you all this? Because I want to thank every one of you here today for taking time out of your busy schedules to learn about HHT, to research HHT, to treat HHT, and to listen to my story today. It means the world to me and all other HHT patients that the dedicated doctors sitting here today want to learn more about this sometimes cruel disease. I would also like to thank Anette and the rest of the HHT team in Denmark for their great cooperation, for taking the time to listen to us patients and for so kindly attending our members' meetings every year.

I would also like to point out how important and productive our work with the 12 HHT organisations in HHT Europe has been over the past 11 years. Supporting each other's patient-centred goals with resources, training and know-how helps us to move forward faster together. As you can see, the development of treatments has improved over the generations of my family. This gives me hope for my old age and for the quality of life of my children and, hopefully, my grandchildren.

My two oldest children have HHT and moderate nose bleeds. They are 22 and 18. What about me? I live a fairly normal life – for now – with HHT. I have telangiectasias in my brain, nose and liver. Yes, I get tired more easily, have my nose lasered when it bleeds and take daily diuretics. Nevertheless, I have a good full-time job, a loving family and good friends. I travel, I go to concerts and I party like everyone else. I strive to do all these things because I decided this disease would not control my life. I will fight it, and I have fought it, for me, for my father and my children.

Once again, THANK YOU for sitting here today and thank you for listening!

Take home message:

- Every HHT patient have their own story, one important part is to learn to live with HHT

HHT and the nose: Epistaxis in HHT - occurrence and treatment options

Prof. Urban Geisthoff

Epistaxis is the most frequent manifestation of HHT and can severely impact quality of life. The primary preventive measure is humidification of the internal nose to prevent crust formation, thereby avoiding trauma, bleeding, and the development of new telangiectases. Humidification can be done by inhalations, irrigations, topically applied ointments, gels, oils, and creams. Currently, only propranolol has demonstrated effectiveness when used topically, while the potential efficacy of tranexamic acid, though suggested by the author, remains unproven.

Other topical options are self-packing (especially with pneumatic low-pressure packings), temporal closure (e.g., using band-aids or soaked cotton balls), or compression of the outer nose through hand pressure or nasal clips. According to the guidelines, the subsequent conservative step involves the use of tranexamic acid in tablet form, supported by robust evidence from two independent high-standard studies.

Endonasal coagulation of the telangiectases has been used for a long time and often successfully. Using the Nd:YAG laser is mentioned in the largest group of studies on this topic. However, the relative efficacy of this method compared to others remains unknown. The final conservative step is the use of Bevacizumab (Avastin®), an antibody initially used for cancer treatment. Administered intravenously, it is generally well-tolerated, yet a rare case reported a fatal lung bleed associated with its use in HHT.

Thalidomide, mentioned alongside Bevacizumab in the guidelines, is not favored by the author due to a Dutch study revealing side effects, including painful or numb fingers, leading to discontinuation by half of the patients after 5 years. Instead, tamoxifen is preferred by the author for its stronger evidence of efficacy.

International guidelines rank surgical techniques such as septodermoplasty and nasal closure at the same level as Bevacizumab. Septodermoplasty involves removing the affected nasal mucosa and replacing it with skin or mucosa from other body regions. While the author has performed this procedure, it is not generally recommended due to irreversibility and associated side effects, including nasal dryness, crusting, and a narrowed airway.

Nasal closure, a radical method resulting in the inability to smell and obligatory mouth breathing, is the only method that, in a significant number of patients, can lead to a complete cessation of epistaxis, even in the presence of anticoagulation. Published studies demonstrate an increase in hemoglobin levels and a clear improvement in the quality of life for affected patients. Unlike septodermoplasty, nasal closure is generally reversible.

The choice of epistaxis treatment methods should be a collaborative decision between the patient and physician, considering the individual circumstances of the patient.

HHT and the lungs: Pulmonary AVM diagnosis and treatment

Dr. Hans-Jurgen Mager

Pulmonary arteriovenous malformations (PAVMs) are direct connections between pulmonary arteries and veins, resulting in a right-to-left shunt (RLS). Symptoms of PAVMs are linked to the RLS and include hypoxemia (especially in cases of large or diffuse PAVMs), clubbing, and migraines. Although PAVMs are mostly asymptomatic, they can lead to severe, potentially life-threatening complications such as stroke and brain abscess due to paradoxical (septic) emboli. Given these serious consequences, screening for PAVM and treatment, if technically possible, are warranted.

The first step of screening involves transthoracic contrast echocardiography (TTCE), which detects an RLS using microbubbles that typically trapped in pulmonary capillaries but can pass through PAVMs. Quantification of the RLS with TTCE can be done on the basis of the relative opacification of the left ventricle (as described by Barzilai et al), the number of microbubbles appearing in the left ventricle (as described by Van Gent et al), or gray scaling (as described by Kroon et al). Grading based on the number of bubbles in the left ventricle is simple and has a high interobserver agreement. The scale ranges from 1 to 3 – grade 1 when number of bubbles in a still frame ranges from 1-29 bubbles, grade 2 when the number ranges from 30-100 bubbles, and grade 3 when the number is more than 100 bubbles. According to international guidelines, a CT-Thorax should be performed in the presence of an RLS, and patients should use antibiotics before non-sterile procedures to prevent brain abscess.

However, a study by Velthuis et al in 2014 showed that a grade 1 RLS is not associated with treatable PAVMs on CT and does not increase the prevalence of stroke or brain abscess, as shown in a large cross-sectional study (Velthuis et al, 2013). The prevalence of PAVMs in HHT varies between countries and regions. In the Netherlands, PAVMs (on CT) occur in about 60% of patients with HHT-I and 10% of patients with HHT-II. PAVMs are treated with embolization of feeding arteries when technically feasible, mostly when the feeding artery's diameter exceeds 2 or 3 mm. Coils or plugs are placed as close to the venous sac of the PAVM as possible, sometimes within the sac. Success rates of embolization in the literature differ from 75 to 100%, due to different definitions of successful embolization (e.g., > 70% shrinkage of venous sac or absence of contrast in draining veins).

Persistence of the PAVM after embolization is mostly caused by persistent perfusion from the pulmonary artery, but it can also result from perfusion from the systemic circulation. Recent studies suggest a role for TTCE not only in PAVM screening but also in evaluating the success of embolization (HHT conference 2022). In three studies, none of the patients with a grade 0 or 1 shunt six months after embolization required repeat treatment. In most HHT centers, TTCE and/or CT are repeated every five years after the initial "negative" screening or in cases of small untreatable PAVMs because PAVMs can grow slowly over time. A large study by Hessels et al in 2022 demonstrated that a longer screening interval (10 years) is safe when a patient shows no RLS at the initial screening.

HHT and the liver: Hepatic arteriovenous malformations

Prof. Elisabetta Buscarini

Hepatic VMs are observed in up to 74% of HHT patients. They are more common and tend to be more severe in HHT2. The average age at the diagnosis of liver VMs is 48 years, and it is more prevalent in females. Doppler ultrasound of the liver is the first-line imaging technique in HHT patients.

Echocardiography should be performed if liver VMs are found to provide information on their hemodynamic consequences. Liver biopsy should be avoided due to the risk of bleeding. Liver VMs typically manifest as small diffuse lesions throughout the liver, rather than discrete large VMs. Three types of intrahepatic shunting can occur: 1) hepatic artery to hepatic veins; 2) hepatic artery to portal veins; and 3) portal veins to hepatic veins. These shunting types result in different and potentially overlapping clinical features, including portal hypertension with ascites and variceal bleeding, biliary ischemia with possible subsequent necrosis, and high-output cardiac failure (HOCF). Changes in liver perfusion may also lead to nodular regenerative hyperplasia and focal nodular hyperplasia.

Only 8% exhibit symptoms at the time of HAVM diagnosis, with average mortality and morbidity rates of 1.1 and 3.6 per 100 person-years, respectively, in a longitudinal cohort. Predictors for the development of significant disease from liver VMs include HHT 2 genotype, stage IV liver VMs (as shown by Doppler ultrasound), both prospectively developed. Retrospective analysis has identified additional factors predicting significant disease: age at presentation over 47 years, female gender, hemoglobin at presentation, and serum alkaline phosphatase over 300 IU/L.

Medical therapy successfully manages symptomatic hepatic VMs in 63% of individuals. Liver transplantation (LT) is the only potentially curative option for patients with symptoms from hepatic VMs (including high output cardiac failure) unresponsive to intensive medical management. Referral for LT consideration in patients with symptomatic complications, particularly those experiencing refractory HOCF, biliary ischemia, or portal hypertension should be considered. Outcomes post-LT in hepatic HHT are favorable, with good 5-year and 10-year survival rates (82-92%).

For those failing medical therapies and deemed unsuitable for LT, there has been an increasing use of Bevacizumab, a recombinant humanized monoclonal antibody designed to inhibit tumor-induced neo-angiogenesis through VEGF inhibition.

HHT and the Heart: Pulmonary hypertension, right sided heart

Dr. Sanne Boerman

Pulmonary hypertension is as a complication of HHT in 8-23% patients, with high output cardiac failure being the most frequent, while pulmonary arterial hypertension (PAH) is less frequent. Pulmonary hypertension is defined as an increase in pulmonary arterial pressure (mPAP) >20mmHg, assessed through right heart catheterization (RHC). Patients with pulmonary hypertension exhibit non-specific symptoms like dyspnea, fatigue, palpitations, and fluid retention. The global population's prevalence is 1%, and the guidelines provide a clinical classification which divides patients into 5 different categories. HHT patients can develop pulmonary arterial hypertension (PAH, WHO group 1) and pulmonary hypertension associated with left heart disease (WHO group 2).

Assessment involves echocardiography for patients with disproportionate symptoms for HHT. Those with intermediate or high probability of pulmonary hypertension, based on factors like peak tricuspid regurgitation velocity and signs such as right ventricle dilation, should undergo RHC. Hemodynamics measured in RHC classify the type of pulmonary hypertension. Patients with PAH have elevated mean PAP, low or normal wedge pressure (<15mmHg), elevated PVR (>2 WU), and diminished or normal cardiac output. Patients with high output cardiac failure exhibit elevated mean PAP, elevated wedge pressure, high cardiac output, and normal to slightly elevated PVR.

PAH is a rare disease but more frequent in HHT patients than those without HHT. There is pulmonary vasculopathy that leads to right heart failure. It is most frequently described in combination combination with AVRL1 mutation and less frequently with ENG mutation. There is no cure, and without treatment, patients deteriorate rapidly, with survival considered worse than PAH alone: 1 and 3-year survival in patients with PAH-HHT is 78% and 53%, compared to 91% and 74% in patients with idiopathic PAH. Treatment should include general measures such as correcting anemia and iron deficiency, fluid and salt restriction, hypoxemia correction, diuretics, and rehabilitation. Closure of PAVM does not elevate mean PAP. Treatment decisions for this specific patient group should follow guidelines and consider disease severity. Vasodilatation therapy may lead to excessive bleeding and increased cardiac output.

High output cardiac failure results from hepatic arteriovenous malformations, causing shunting of oxygenated blood from hepatic arteries to hepatic veins, bypassing the liver. This activates the sympathetic nervous system and RAAS axis, increasing cardiac output. An increased cardiac output leads to increase in mean PAP, estimated up to 0.5 to 3.0 mmHg per liter/min CO. Pregnancy and anemia can exacerbate this condition. A high output state elevates pulmonary pressures and enlarges the left atrium, putting patients at risk for right heart failure and atrial fibrillation. Treatment involves supportive care, Bevacizumab, Tacrolimus, and liver transplantation. Post-transplantation, patients have a 5- and 10-year survival of > 80%. Disease recurrence occurs, with a median interval of 10 years and a cumulative incidence of 48% at 15 years.

HHT and multidisciplinary approach and challenges

Prof. Carlo Sabba

Rare Diseases (RD) encompass a diverse group of pathological conditions characterized by low prevalence in the general population. The definition of 'rarity' has evolved throughout the history of medicine and epidemiology. Currently, a disease is considered "rare" in the European Union population if its prevalence is below 1:2,000 individuals. Despite being neglected and labeled as "orphan diseases" for a long time, RDs are now gaining increased attention in the medical and scientific community. Managing RDs presents numerous challenges, including limited effective treatments, insufficient familiarity among medical professionals, financial constraints for research, and difficulties in delivering adequate healthcare. The complexity is heightened by the multi-organ involvement seen in most RDs, making it challenging to provide proper management.

Hereditary Haemorrhagic Telangiectasia (HHT) is a rare vascular disorder with multi-organ involvement, and it encounters many of the issues associated with RDs when establishing healthcare pathways. For decades, a single-organ approach has been adopted for HHT, focusing on specific clinical histories, manifestations, or complaints. However, proper HHT management requires a comprehensive multi-disciplinary approach, which poses its own set of challenges.

HHT is characterized by malformations in the structure of blood vessels, affecting many organs due to the ubiquitous distribution of blood vessels throughout the body. Arterio-venous malformations (AVMs) can not only cause clinical features in the involved organ but also lead to secondary consequences in functionally related, potentially AVM-free areas. Failure to address the multi-organ nature of HHT may result in delayed diagnosis, with some patients experiencing a diagnostic time lag of 14-25 years from disease onset to the correct diagnosis.

Focusing on a single organ or aspect of a multi-organ disease without a holistic multidisciplinary approach may lead to a failure in providing the comprehensive management needed for a multi-organ rare disease like HHT. The tendency of specialists to focus on their specific area of expertise may contribute to missing the broader healthcare perspective needed for these complex conditions.

Dr. Robert I White, the past Director of Vascular Malformation Clinical and Research Group at Yale University, advocated for the development of multidisciplinary Centers of Excellence for HHT worldwide. Encouraging the recruitment of specialists in Internal Medicine, who excel in coordinating various special examinations into a coherent view, can enhance the multidisciplinary approach. The multidisciplinary HHT Center in Bari, Italy, is an example of such a model, founded through collaboration between Dr. Robert I White, an Italian specialist in Internal Medicine, and a patient's group leader from the same town.

VASCERN Referral Centers, including those in the HHT-Working Group, offer multi-disciplinary care for HHT based on the best available evidence. VASCERN aims to provide proper training for newly-established emerging Centers in countries lacking proper healthcare for HHT patients. Experience from established VASCERN Referral Centers suggests that a multidisciplinary model increases the ability to recognize underascertained patients, reduces underdiagnosis, and facilitates staff education and formation.

HHT and gastrointestinal bleeding

Annette Dam Fialla, Jens Kjeldsen

Gastrointestinal telangiectasia may be present in both sub-types of HHT. The diagnosis is obtained by upper endoscopy, colonoscopy, or capsule endoscopy. The telangiectatic lesions may cause bleeding and iron deficiency with or without anaemia. The treatment offered depends on the degree of iron loss and anemia, and the presence of bleeding. The treatment strategies range from iron supplements over endoscopic treatment to systemic treatment. A non-contact procedure such as argon plasma coagulation may be preferred when endoscopic therapy is needed, although other endoscopic treatment options can be applied. If supportive therapy and endoscopic treatment are insufficient or not possible (extensive intestinal involvement and in areas difficult to reach – small bowel), systemic treatment may be offered (1). Several treatments have been used, with different outcomes and adverse event profiles. For the time being bevacizumab seems to be the most efficient treatment with a reasonable adverse event profile (2).

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HHT and anaemia

Prof. Claire Shovlin

Anaemia is functionally defined as the "insufficient mass of red cells to deliver oxygen adequately to tissues," where red cells contain the necessary haemoglobin for oxygen transport. The most common anaemia pattern in HHT results from inadequate haemoglobin production, leading to smaller red blood cells with less haemoglobin per cell (Santhirapala-PlosOne-2014). Nutrient supply (iron/B12/folate) required for haemoglobin production is compromised by HHT bleeding. Normal bone marrow and red cells/haemoglobin are necessary for adequate haemoglobin production, but these become issues in HHT only if patients have other genetic variants (Joyce-Blood Adv-2022).

Meeting normal dietary iron requirements can be challenging, especially for pre-menopausal women, and is even more difficult with regular nosebleeds or gastrointestinal bleeding in HHT. Therefore, our first approach to anaemia management is helping individuals understand their haemorrhage-adjusted iron requirement (Finnamore-PlosOne-2013) and whether this, along with dietary and therapeutic iron intake, explains the pattern of their full blood count and iron indices pattern.

A rarer HHT-specific cause of anaemia is accelerated destruction of red cells in circulation, more common in HHT patients with established severe anaemia already on iron treatments, which can be suspected and proven if anaemia is out-of-proportion to expected iron deficits (Thieleman-Haematologica-2019). Wider causes of anaemia, such as menorrhagia and other iron losses, thalassaemia, and other haemolytic anaemias, should also be considered.

Anaemia is important for everyone because it results in low arterial oxygen content (CaO2) and higher cardiac outputs, leading to reduced exercise capacity, breathlessness, palpitations, and even angina. Anaemia is particularly important in HHT, where low systemic vascular resistance due to systemic arteriovenous malformations (AVMs) already increases cardiac outputs, and wwhere anaemia can provoke decompensated high output cardiac failure for HHT patients with hepatic AVMs (Buscarini-DigDisSci-2011). These interactions are explained in VASCERN's 2022 Frameworks manuscript (Shovlin-EurJHumGenet-2022).

In HHT, anaemia is usually due to iron deficiency, leading to 'stickier' blood. Iron deficiency in HHT is linked to more venous thromboemboli (Livesey-Thorax-2012) and more ischemic strokes for people with pulmonary AVMs (Topiwala-Neurology-2022). Anaemia is associated with lower exercise capacity (Gawecki-BMJOR-2019) and higher anesthetic risks (Thurairatnam-medRxiv-2020). However, iron treatments can lead to higher blood iron levels, carrying risks. In one HHT series, 10% of iron users (oral and intravenous) reached a blood level normally used to recommend removal of body iron, and higher iron levels/intravenous iron use were associated with a higher risk of brain abscess for those with pulmonary AVMs (Boother-ClinInfectDis-2017).

The first-line diagnostic assessment to inform anaemia management in a general HHT service is to measure the full blood count, serum iron, transferrin saturation index (TfSI), and ferritin. In simple iron deficiency anaemia, there will be low haemoglobin (Hb), MCV, MCHC, MCH, ferritin, serum iron, and TfSI. If iron deficiency is evident (low ferritin, serum iron, and TfSI) but the Hb is normal, consider if this is "low" for a patient with pulmonary AVMs, who needs higher Hb to compensate for low oxygen saturation (SaO2) measured by pulse oximetry. If other patterns are present, referral for haematological assessment is encouraged to identify whether there are additional, non-HHT causes of anaemia for the patient.

Treatment of iron deficiency is usually long-term unless ongoing bleeds can be limited. Recent work emphasizes lower strength (<60mg elemental iron) tablets to enhance iron absorption and reduce gastrointestinal side effects that affected ~50% of iron users with HHT (Finnamore-PlosOne-2013). Daily 35mg oral elemental iron can correct mild-moderate anaemia in HHT (Rizvi-AnnAmThoracSoc-2017) and can be adjusted upwards, rather than starting high. If patients do not improve or cannot tolerate oral iron, then intravenous iron is appropriate (Faughnan-Annals-2020). In our experience, once started on iron infusions, these are required more frequently even when bleeding is no longer an obvious cause (Thielemans-Haematologica-2019). Ongoing evaluation is required to assess if regular treatments remain appropriate or need adjustment.

Red cell transfusions are required where anaemia is severe. That "severity" level is reached earlier in HHT due to ongoing bleeds and/or higher cardiac demands. In the 2020 International Guidelines, a lower threshold for red cell transfusion in HHT was proposed by the Anaemia subcommittee (Faughnan-Annals-2020).

New horizon questions include why iron treatments aggravate nosebleeds in ~1 in 20 people with HHT (Shovlin-Laryngoscope-2016; Shovlin-ERJOR-2016); how important are differences by HHT genotype (Rizvi-Haematologica-2023); and why new unexplained coagulation profiles mapping to thrombotic phenotypes seen in HHT are identified by machine learning algorithms that also detect expected haemorrhage relationships (Mukhtar-eJHaem-2023). Further research is needed to optimize the management of anaemia, a critical determinant of health in HHT.

HHT and pregnancies: the pregnant HHT patient

Prof. Olivier Dupuis-Lebreton

The goal was to provide evidence-based information on HHT and pregnancy to empower patients and doctors in preventing maternal and neonatal morbidities and mortalities. The data presented are based on studies from a PubMed review and our study, published in BJOG[1].

Are women with HHT at a higher risk during pregnancy? Studies indicate that maternal death rates account for 1.2% of pregnancies and 3.2% of affected women. Life-threatening maternal events occurred in 2.7 to 6.8% of pregnancies, with fetal deaths also observed. The data suggest that pregnancies with HHT pose high risks from both maternal and fetal perspectives. Therefore, women with HHT should be monitored by an obstetrician in collaboration with an HHT center.

During pregnancy, are patients informed that they have HHT? Studies show that 71% of HHT patients exhibit some evidence of the condition by the age of 16 years[2], and 50% of patients develop cutaneous telangiectasia by the age of 30 years[3], with epistaxis (> 4 per year) typically emerging in the second decade. However, research indicates that only 11 to 26% of women with confirmed HHT are aware of their disease before the first pregnancy[1,4,5]. Pregnant women reporting more than 4 epistaxis episodes a year should undergo screening for lip, tongue, and finger pad telangiectasias, as well as finger clubbing. Those with these symptoms should be promptly referred to an expert HHT center.

Are there any "red flag symptoms" that patients and obstetricians need to be aware of? Yes, coughing up blood or experiencing sudden dyspnea or thoracic pain may be related to complications of PAVMs. These symptoms require immediate referral to an emergency center and an HHT center.

Is there anything special that needs to be monitored in a pregnant woman with HHT? Yes, maternal oxygen saturation rate, hemoglobin level, and fetal growth should all be closely monitored.

Are the complications of pulmonary AVMs a problem during pregnancy? Pulmonary AVMs, present in 50% of HHT patients, can lead to hemothorax or hemoptysis with an 8% risk of rupture[6]. This poses a risk of cerebral abscess, ischemic cerebral stroke, and transient cerebral ischemic attack via paradoxical emboli in the mother, and to intrauterine growth restriction (IUGR) or fetal death in case of severe hypoxemia. It's crucial to note that 90% of severe events during pregnancy are PAVM-related[1,7], with rupture described as early as 19 weeks gestation (WG)[6].

Is it possible to perform pulmonary embolization during pregnancy? Pulmonary embolization can be performed from 16 WG to term, with the maximum recommended exposure being 500 mrad. The fluoroscopy time and estimated fetal radiation dose should be as low as possible, emphasizing that embolizations should only be performed by an expert team[8].

Are hepatic AVMs dangerous during pregnancy? Thirty percent of HHT patients have hepatic AVM, with 95% being asymptomatic[11]. During pregnancy, 0 to 11% of severe events are HAVM-related[1,7].

Are cerebral AVMs dangerous during pregnancy? The 3.5% risk of primary hemorrhage from a CAVM of any etiology during pregnancy does not differ from the annual bleeding rate of non-gravid women[9,10]. Therefore, it is recommended to avoid a prolonged second stage during delivery for patients with HHT, as well as Valsalva maneuvers.

Is hemorrhage from spinal AVMs a problem during delivery for pregnant women with HHT? Studies show that the rate of spinal AVMs is less than 0.5%, and no cases of spinal hemorrhage following epidural analgesia in HHT patients have been reported[1,5,11]. Spinal AVMs in HHT patients are located in the subarachnoid space, making MRI screening unnecessary and allowing for the performance of epidural analgesia.

During pregnancy, which clinician should perform the ultrasounds? In a few cases, a fetus or neonate has been diagnosed with PAVMs[12]. Therefore, during pregnancy, the ultrasonographer should be aware that PAVMs can be diagnosed prenatally in a fetus, requiring specialized neonatal care.

Is prenatal genetic diagnosis of HHT necessary? No, having HHT is not an indication for prenatal diagnosis.

Is the discovery of HHT during pregnancy an indication for termination of pregnancy? No, the discovery of HHT is not an indication for termination of pregnancy.

Is HHT a contraindication to pregnancy? No, but it is advisable to perform a full assessment of the disease at an HHT expert center before starting a pregnancy.

Is HHT an indication for systematic Caesarean section? No, the presence of HHT is not an indication for systematic Caesarean section. Cases where Caesarean section is necessary due to HHT are rare.

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HHT and children: At what age is screening for HHT relevant

Dr. Sophie Dupuis-Girod

If we consider the general issues for children with HHT, we can clearly see that evidence-based medicine in children with the condition is scarce. Most children are effectively asymptomatic, there are only a few pediatric studies, and these studies contain many biases. In general, HHT is not apparent at birth but instead evolves with age. Epistaxis are frequent (50 to 92%) but unspecific during childhood, and telangiectases develop and worsen with age, becoming more prevalent in each individual with time[1–3]. Two types of arteriovenous malformations (AVMs) - pulmonary AVMs and cerebral or spinal AVMs - can be responsible for rare complications during childhood in HHT. Both are more frequent in HHT1 (related to the ENG mutation)[4–7].

The prevalence of PAVMs is similar in children and adults and most PAVMs can be present at birth. PAVM development is thought to be complete by the end of puberty[7]. After puberty, de novo formation of PAVMs over time is unlikely. All children with small PAVMs, and most children with large PAVMs, had no related clinical symptoms. Rare symptoms are related to hypoxemia (growth retardation, cyanosis, exercise intolerance, hemoptysis, chest pain, shortness of breath) or paradoxical embolism (strokes and cerebral abscesses), but in asymptomatic children with normal SaO2 no paradoxical embolic strokes or cerebral abscesses have been described before puberty.

The screening for PAVMs in asymptomatic children with HHT is recommended [8] for preventing complications, but the best time to screen for PAVMs is not known and differs from one country to another in Europe. Transthoracic contrast echocardiography, or chest radiography and pulse oximetry are both used. Screening with CT in children is not recommended. International guidelines recommend treating large pulmonary AVMs and pulmonary AVMs associated with reduced oxygen saturation in children to avoid serious complications[8]. It has been shown that trans catheter embolization is safe and effective[9], but the long-term outcome of embolization of PAVMs in children with HHT is still far from clear. The technique may not be as good as previously thought as there is a risk of hemoptysis secondary to systemic arterial collateral supply which must be evaluated.

Brain and spinal vascular malformations affect approximately 10% of HHT patients and are thought to be complete during childhood in most cases. Their prevalence and complications are nevertheless highly variable from one series to another[10–13]. Furthermore, these AVMs span multiple subtypes in HHT: nidus-type cerebral AVMs, capillary telangiectases, arteriovenous fistulas (AVF), cavernous malformations, and spinal AV fistulas[10]. The frequency of these subtypes differs in relation to age. AVF are observed in young children (before the age of 5 years). They are very rare but have a high risk of bleeding. Nidus-type AVMs are present in young adolescents, and in young adults, micro AVMs are the most frequent with a very low risk of bleeding[14–16].

Treatment is recommended in all cases after bleeding or in the case of high risk VMs, but the risks of treatment are not negligible, and a case-by-case discussion in expert centers is necessary regarding treatment.

Screening for brain and spinal AVMs is highly debated. Current evidence does not favor the treatment of unruptured cerebral AVMs, and therefore cannot be used to support widespread screening of asymptomatic HHT patients[15]. This position is different from the International Guidelines where the expert panel recommends screening for brain VM in asymptomatic children with HHT or at risk of HHT, at the time of presentation/diagnosis[8]. More data from large, unbiased prospective cohorts is necessary.

Liver AVMs worsen with age and no symptoms related to liver AVMs have ever been described during childhood although asymptomatic HAVMs have been reported[17]. No screening for liver AVMs is recommended during childhood.

Digestive telangiectases are not responsible for GI bleeding in children with HHT1 or 2. They can be observed in HHT/JP syndrome related to the SMAD4 mutation. For SMAD4 patients, it is recommended that colonoscopic and upper endoscopic surveillance be initiated at age 12–15 years, or earlier if symptomatic. Genetic testing is offered to asymptomatic children of a parent with HHT but age at genetic testing differs between countries.

Take Home Message

- Most children are asymptomatic and have a normal life with symptoms tending to develop in late childhood.
- Multiple reports of cerebral and pulmonary AVMs in children have been published; however, the exact prevalence of such AVMs has not been established.
- In all cases, a careful clinical examination that includes measuring oxygen saturation and looking for murmurs with pulmonary and cerebral auscultation is necessary at birth and during childhood.
- For asymptomatic children

- screening for PAVMs with pulse oximetry or echo bubble before puberty.
- screening for CAVMs is still subject to debate.

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HHT and psychological aspects

Sylvie Fourdrinoy

HHT has specific characteristics that affect the way patients perceive and live with the disease. It is a genetic disease that cannot be cured and is inherited through the family. It is a rare disease, which can lead to feelings of isolation and a lack of knowledge and understanding, including from professionals. Whether visible or invisible, symptoms can develop and affect quality of life.

The moment when the diagnosis is announced is particularly sensitive because, although it provides an answer to the cause of the symptoms, it can be perceived as bad news, an indication of a negative outcome. The impact of the announcement is always unique and depends on the context, the patient's family and personal history, etc. Other times can also be more difficult: puberty, pregnancy plans, worsening of symptoms, etc.

Living with HHT can be difficult and these difficulties are not always directly related to the severity of the symptoms, but rather to the patient's experience, which depends on their personal and family history and representations.

Psychological support may therefore be needed, and it is important not to hesitate to discuss this with patients. The use of psychological support, although not systematic and compulsory, can be a help in difficult moments. Asking for psychological support is not a sign of weakness, but of self-care.

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