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PRACTICE GUIDELINES

Hereditary hemorrhagic telangiectasia and liver involvement
Vascular liver diseases: position papers from the francophone network for vascular liver diseases, the French Association for the Study of the Liver (AFEF), and ERN-rare liver

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Abbreviations: ALK-1, activin receptor-like kinase 1; CT scan, computed tomography scan; Doppler US, doppler ultrasound; ENG, endoglin; FNH, focal nodular hyperplasia; HA, hepatic artery; HHT, hereditary hemorrhagic telangiectasia; HOCF, high output cardiac failure; HVM, hepatic vascular malformation; MRI, magnetic resonance imaging; PFV, peak flow velocity; RI, resistance index; TGF, transforming growth factor; UDCA, ursodeoxycholic acid; VEGF, vascular endothelial growth factor; VM, vascular malformation.

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Hereditary hemorrhagic telangiectasia;
Liver;
Portal hypertension;
Rendu-Osler-Weber

Introduction

Rendu-Osler-Weber disease or hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant genetic disorder, characterized by vascular malformations affecting predominantly the skin, lungs, brain, liver, and gastrointestinal tract. The estimated prevalence ranges from 1 per 5,000 to 1 per 10,000. In France, the prevalence of HHT varies greatly between regions. The clinical presentation of HHT ranges from asymptomatic to life-threatening cases, according to the age, number and location (mainly cutaneous, mucosal and viscera) of telangiectasia vascular malformations (VM). An experienced multidisciplinary team is needed for early diagnosis and optimal management of these patients.

How to perform the diagnostic and the initial evaluation of HHT and liver involvement?

How are the clinical diagnostics and genetics of HHT characterized?

Hereditary Hemorrhagic Telangiectasia (HHT) is characterized by multiple mucocutaneous and visceral VM. The diagnosis of HHT is clinical and confirmed by a genetic test. This genetic testing helps clarify the genetic status of asymptomatic at-risk family members.

Diagnosis relies on clinical diagnostic criteria, known as the Curaçao criteria (Table 1). HHT is confirmed when at least three criteria are present; possible or suspected when 2 criteria are present; and is unlikely when only 1 criterion is present in an adult patient [1].

The endoglin gene mutation (*ENG*; Online Mendelian Inheritance in Man (OMIM) 187300) and activin A receptor type II-like gene mutation (*ACVRL1* or *ALK1*, OMIM 600376) are responsible for types I and II HHT, respectively. These two mutations are responsible for about 90% of symptomatic HHT cases. Hepatic malformations are more frequent in HHT type 2. Mutation in the gene *MAHD4* coding for the transcription factor Smad4, is responsible for HHT combining juvenile polyposis. There may be marked intrafamilial clinical variations or among subjects who carry the same mutation, suggesting the influence of sex, age and the presence of modifier genes [2].

A genetic analysis is offered to the proposant if clinical diagnosis is definite or possible including ALK1, ENG, SMAD4, EPHB4 and RASA1 gene analysis.

Table 1 Curaçao criteria for Hemorrhagic Hereditary Telangiectasia (HHT): definite diagnosis: ≥ 3 criteria; possible diagnosis: ≥ 2 criteria; unlikely diagnosis: < 2 criteria.

Clinical criteria	Description
Epistaxis	Spontaneous and recurrent nose bleed
Telangiectasia	Multiple at characteristic sites: lips, mouth, fingers, nose
Visceral lesions	Gastro-intestinal, pulmonary, hepatic, cerebral or spinal VM (with or without bleeding)
Family history	First degree family member with a diagnosis of HHT according to these criteria

HHT: hemorrhagic hereditary telangiectasia; VM: vascular malformations.

Genetic testing can help to confirm the diagnosis in patients with mild symptoms who do not meet all Curacao criteria, or to perform genetic testing in the relatives of the index case who has been identified with the corresponding mutated gene by genetic testing. The first recommendation is to send the index case for genetic counseling to identify the causal mutation and further screen for the mutation in the family. Genetic testing is proposed to all relatives [3].

What types of hepatic vascular malformations can be found and how do they impact clinical features?

Hepatic vascular malformations (HVM) are frequent, diagnosed with Doppler US or CT scan in 32% to 84% of the patients with type 2 HHT [3—6]. Published data on the natural history of HHT show that HVM are symptomatic in 10% of patients at diagnosis, but the average incidence rates of death and complications are 1.1 and 3.6 per 100 person-years [7]. VMs unique to HHT are diffuse in the liver, and highly variable, from small telangiectasia to very large VM [5]. The different severities of liver VMs [6,7] explain the high variability of clinical symptoms.

Symptomatic or asymptomatic HVM are more frequent in type 2 HHT with a large predominance in women. Symptoms are more frequent after the age of 50 [8,9]. Liver enzymes are usually only moderately elevated, with normal transaminases (AST/ALT) while γ-glutamyl transpeptidase is often elevated. Thus, there is no hepatocellular insufficiency. In case of hepatocellular insufficiency, acute heart failure or another common cause of liver failure (drug induced, viral, auto-immune..) needs to be investigated.

Three types of shunts can co-exist:

- Arterio-systemic shunts (from the hepatic artery to the hepatic vein) are most frequent (> 70% of symptomatic liver lesions) and can cause high cardiac output followed by high output cardiac failure and finally, pulmonary hypertension (most frequently post-capillary after many years of progression), resulting in an increased risk of arrhythmia and atrial fibrillation. These complications usually progress slowly over many years [10,11]. The main symptom is exertional dyspnea followed by dyspnea at rest, which increases very slowly before the clinical signs of cardiac failure develop;
- Arterio-portal shunts (from the hepatic artery to the portal vein) can cause portal hypertension with a risk of developing ascites and bleeding from ruptured esophageal or gastric varices;
- Porto-systemic shunts (from the portal vein to the hepatic vein) are responsible for hepatic encephalopathy.

All the shunts from the hepatic artery to the portal or hepatic veins result in an arterial mesenteric steal syndrome with a risk of intestinal ischemia. Patients with a replaced right hepatic artery (arising from the superior mesenteric artery) are more prone to this complication. Because the biliary tract is exclusively vascularized by the hepatic artery, arteriovenous shunts can cause biliary ischemia leading to biliary necrosis. Biliary necrosis is associated with cholestasis, stenosis, biliary extravasations forming bilomas and sometimes cholangitis.

Focal or diffuse HVM are also responsible for increased arterial perfusion and decreased portal perfusion as well as increased regenerative activity, leading to the development of focal nodular hyperplasia [12] and/or regenerative nodular hyperplasia.

How to confirm the diagnosis of hepatic vascular malformations and which complications may occur?

Several lesions can be identified in HHT on contrast-enhanced imaging (mostly CT and MRI).

Increased diameter of hepatic arteries

This finding is seen in most patients with hepatic involvement. Diffuse enlargement is very suggestive of HHT. Indeed, other diseases such as cirrhosis may increase hepatic artery diameter but not as significantly.

Telangiectases are the most common hepatic lesions and may be focal or diffuse

They are rounded, hypervascular lesions, usually subcentimetric. They appear as focal hyperenhancing lesions in the arterial phase and often become isoattenuating/isointense on CT and MR imaging on delayed phase acquisitions. [13]. Telangiectases may coalesce to form large confluent vascular masses.

Arteriovenous (hepatic artery to hepatic vein) shunts are the most frequent vascular shunts in HHT

Visualization is better during the arterial phase with early enhancement of hepatic veins.

There is early enhancement of the portal vein during the arterial phase in the presence of arterioportal (hepatic artery to portal vein) shunts

Indirect signs such as wedge-shaped hyperenhancing areas are found during the arterial phase in the presence of small shunts.

Portovenous (portal vein to hepatic vein) shunts are rare in HHT and not easy to visualize

They may be identified during the portal venous phase with direct communication between a branch of the portal vein and a hepatic vein.

Benign regenerative nodules that mainly correspond to FNH-like lesions

The diagnosis is based on conventional imaging. On contrast-enhanced CT/MR imaging, telangiectases may mimic FNH-like lesions because both are hyperenhancing during the arterial phase. Nevertheless, unenhanced and hepatobiliary phase acquisitions using MR hepatospecific agents can differentiate both.

Three types of situations may be encountered:

- diagnosis of HHT is certain, and the patient does not have any signs suggesting HVM. Systematic screening for HVM is recommended by liver Doppler ultrasound [14]. Early diagnosis of HVM allows earlier detection and more effec-

Table 2 Severity grading of hepatic VMs in HHT (according to Buscarini et al. [6]).

VM Grade	
0+	HA Diameter > 5 mm and < 6 mm and/or PFV > 80 cm/s and/or RI < 0.55 and/or Peripheral hepatic hypervascularization
1	HA Diameter > 6 mm, only extrahepatic, and/or PFV > 80 cm/s and/or RI < 0.55
2	HA dilatation, extra- and intrahepatic (''double channel'' aspect) and PFV > 80 cm/s Possibly associated with moderate flow abnormalities of hepatic and/or portal veins
3	Complex changes in hepatic artery and its branches (tortuous and tangled) with marked flow abnormalities associated with: moderate dilatation of hepatic and/or portal vein and/or abnormality of hepatic and/or portal vein flow
4	Decompensation of arteriovenous shunt such as: marked dilatation of hepatic and/or portal vein marked flow abnormalities in both arteries and veins

tive treatment of the complications of HHT, especially cardiac;
- diagnosis of HHT is unlikely or only suspected based on Curaçao criteria, and identification of HVM confirms the diagnosis;
- diagnosis of HHT is certain, the patient presents with clinical signs of hepatic VMs, and assessment of HVM can help determine the most appropriate management.

Screening for HVM should be performed by Doppler ultrasound (US) because this technique is accurate (sensitivity 86 to 97%, specificity 100%) for the detection of HVMs, non-invasive, easily available, and inexpensive [6,15]. However, there are no well-designed studies assessing the positive predictive value of Doppler US [3]. As described above there are three types of intrahepatic shunts, and the measurement of the diameter of the hepatic artery, the resistance index and peak systolic hepatic arterial velocity are helpful tools to determine the severity of HVMs (Table 2, [6]).

The prevalence of HVM was found to be between 32% and 72% in screening studies using Doppler US, and between 67% and 78% with multidetector computed tomography (CT) scan [3]. Imaging helps detect small to large, solitary or multiple associated benign tumors which are found in up to 4% of HHT patients (about 100 times more than in the general population (0.03%)) and can be present in the absence of HVM [12,16]. In a series of 30 patients with HHT [17], 47% had multiple liver nodules and all 9 biopsies showed focal nodular hyperplasia (FNH), FNH-like or large regenerative nodules. No hepatocellular adenomas or hepatocellular carcinomas were identified in this series. Indeed, hepatocellular carcinoma seems to be rare in these patients. Once a hypervascular lesion is identified, MR imaging or contrast-enhanced US help characterize the lesions [14,18]. Precontrast and contrast-enhanced MR imaging with hepatobiliary contrast agents can differentiate FNH-like lesions from large telangiectasia. In most cases an evaluation of the patient's history, clinical data and imaging results can confirm the diagnosis of FNH or regenerative nodules [12]. Liver biopsy is associated with a high risk of bleeding and its indication should be discussed with a multidisciplinary panel and should usually be avoided [3,14].

The clinical outcome of HVM depends on the severity of disease. High cardiac output, high output cardiac failure (HOCF), ischemic cholangitis and portal hypertension may be present alone or as co-existing complications. Moreover, other mechanisms can worsen these complications. Indeed, bleeding from telangiectasia, can increase anemia, and exacerbate HVM-induced high cardiac output.

Finally, high cardiac output associated with anemia and/or atrial fibrillation can worsen left cardiac failure, which may be complicated by post-capillary pulmonary hypertension (Table 3) and finally left and right heart failure [19—21]. Precapillary pulmonary hypertension can be also observed in the setting of ACVRL-1 mutation (TGF-ß pathway), this entity belonging to the group 1 of the clinical classification of pulmonary hypertension (1.2. heritable pulmonary arterial hypertension) (Table 3) Portal hypertension can also be associated with precapillairy pulmonary arterial hypertension defining portopulmonary hypertension (Group 1). [19,20].

Echocardiography is performed to estimate pulmonary arterial pressures, to measure right and left atrial and ventricular areas, to assess right and left ventricular hypertrophy. It can also estimate cardiac output with however a poor accuracy. It is also helpful to monitor medical therapy (diuretics, beta-blockers...). In case of suspicion of pulmonary hypertension, confirmation by right heart catheterization is mandatory.

Overall outcome was reported in 154 patients with HHT and HVM after a median follow-up of 44 months. Eight (5.2%) patients died from HVM-related complications, including 2/13 (15%) symptomatic patients and 6/141(4%) asymptomatic patients at diagnosis. All deceased patients had stage 4 liver HVMs at baseline [7]. Determination of the severity of HVM can be useful to tailor patient management and follow-up.

What treatment is appropriate for HHT and liver involvement?

Implicated professional and coordination modalities

Treatment should be multidisciplinary. In complex cases, expert advice is mandatory.

Treatment

No treatment is recommended for asymptomatic patients. There is no prophylactic treatment.

Symptomatic treatment

The symptoms of anemia and bleeding must be treated with iron supplementation or blood transfusions to relieve fatigue and prevent the worsening of other complications. Phys-

Table 3 Haemodynamic definitions of pulmonary hypertension (PH).

Definitions	Haemodynamic criteria	Clinical groups
Pre-capillary PH	mPAP > 20 mmHg PAWP ≤ 15 mmHg PVR ≥ 3 UW	Group 1: PAH Group 3: PH due to lung diseases and/or hypoxia Group 4: PH due to pulmonary artery obstructions Group 5: PH with unclear and/or multifactorial mechanisms.
Isolated post-capillary PH	mPAP > 20 mmHg PAWP > 15 mmHg PVR < 3 UW	Group 2: PH due to left heart disease
Combined pre- and post-capillary PH	mPAP > 20 mmHg PAWP > 15 mmHg PVR ≥ 3 UW	Group 5: PH with unclear and/or multifactorial mechanisms

mPAP: mean pulmonary arterial pressure. PAH: pulmonary arterial hypertension. PAWP: pulmonary artery wedge pressure. PVR: pulmonary vascular resistance. WU: Wood Units (1 WU = 80 dyn.s.cm^{-5}).

ical and psychological support are recommended because HHT strongly impacts the patient's social, physical and psychological well-being [22]. Patient associations may be contacted for support and information on patient management, quality of life and treatment.

High cardiac output, high-output heart failure and heart insufficiency

In patients with exertional dyspnea, cardiac ultrasound should be performed to evaluate cardiac overload and to estimate cardiac index (normal< 4.0 L/min/m^2). Regular cardiac ultrasound monitoring is necessary in patients with cardiac overload.

A cardiopulmonary assessment including right heart catheterization should be performed to determine cardiac function and to confirm and characterize pulmonary hypertension (pre- and/or post-capillary pulmonary hypertension, Table 3). Post-capillary pulmonary hypertension (i.e. pulmonary hypertension due to left heart dysfunction) is confirmed when mean pulmonary artery pressure is > 20 mmHg with pulmonary artery wedge pressure > 15 mmHg [22]. Symptomatic heart failure in HHT should be treated with the same protocols as cardiac insufficiency (salt restriction, diuretics). The level of proof on prognosis is weak.

The use of angiotensin-converting enzyme inhibitors is controversial and should not be recommended. Beta-blockers may be prescribed because of their well-known efficacy for cardiac insufficiency and their antiarrhythmic effect. Although they decrease cardiac output, they may worsen the situation during the terminal stage. In case of atrial fibrillation, anticoagulants should be proposed and their benefit/risk must be assessed for each patient in an expert HHT center.

Portal hypertension and encephalopathy

Treatment of portal hypertension is not specific and is the same as that in patients without HHT. Beta-blockers are usually contraindicated in patients with severe cardiac failure. Transjugular intrahepatic portosystemic shunts are not recommended because they will worsen the hyperdynamic circulatory state and HOCF. In case of encephalopathy, lactulose and rifaximin may be prescribed [14].

Biliary complications

Treatment of cholangitis is not different from that in patients without HHT. Bilomas and especially necrotizing cholangitis are severe complications and OLT should be discussed. UDCA treatment may be considered on a case-by-case basis.

Liver transplantation

When medical therapy fails, liver transplantation is indicated, in particular in patients with intractable HOCF (high cardiac output associated with left cardiac failure, or left cardiac failure associated to high arterial pulmonary pressure), intractable portal hypertension, and severe ischemic cholangitis with or without hepatocellular insufficiency. There are no specific recommendations on the optimal timing for liver transplantation. An accurate diagnosis of portopulmonary hypertension by right heart catheterization is essential before liver transplantation. Pre- and post- surgical mortality varies from 10 to 20% related to bleeding risks and heart failure. Five- and 10-year patient and graft survival varies from 83 to 92% [23]. Recurrence is a late or very late event with an estimated cumulative risk of 17% at 10 years and 48% at 15 years after liver transplantation. Thus, long-term follow up is needed [24].

Medical treatments

Bevacizumab. Dysregulation of angiogenesis in HHT explains the high VEGF and TGF plasma levels. Bevacizumab is an anti-VEGF monoclonal antibody. Several non-randomized studies have shown that this treatment could decrease anemia secondary to bleeding, HOCF and cholangitis [25,28]. A 5 mg/kg IV dosage was used every two weeks for a total of 6 injections followed by one IV injection every three months for a total of 12 months in some studies [25-28]. After bevacizumab was discontinued, recurrent bleeding was observed one month to 2 years later. Bevacizumab could be proposed in older patients or in patients in whom liver transplantation cannot be performed due to the severity of HHT complications.

However, if HHT improves over time, liver transplantation should be reconsidered. Bevacizumab should not delay liver transplantation, especially in older patients, whose age could limit transplantation 2 to 5 years later.
Others. Other treatments such as thalidomide have not specifically been validated in patients with HVM.

Transarterial embolization
The aim of hepatic transarterial embolization is to reduce arteriovenous or arterioportal shunts with embolization of one of the hepatic arterial branches. However, embolization is not effective because HHT presents with diffuse HVMs. Moreover, the effect of treatment is usually transient. Embolization may lead to severe complications such as hepatic or biliary necrosis. Thus, this treatment is not currently recommended.

Recommendations

1. Consider a diagnosis of hereditary hemorrhagic telangiectasia in the presence of diffuse hepatic vascular malformations and a dilated hepatic artery associated or not with marked dilatation of portal and hepatic veins (A1).
2. Screen patients with hereditary hemorrhagic telangiectasia for hepatic vascular malformations (A1).
3. Doppler ultrasound is the first line imaging test for the diagnosis of hepatic vascular malformations. Multiphase CT scan is another option (A2).
4. Characterize nodules on MR imaging or appropriate non-invasive contrast enhanced imaging (B2).
5. Liver biopsy is not required for the diagnosis of hereditary hemorrhagic telangiectasia (A2).
6. Perform echocardiography and determine the cardiac index in patients with liver involvement at baseline and during follow-up (B2).
7. A multidisciplinary approach should be taken to treatment and especially invasive treatment including a discussion in HHT centers with an integrated team of experts (B2).
8. Hepatic transarterial embolization is contra indicated because of the risk of worsening biliary ischemia (B2).
9. Liver transplantation should be discussed when appropriate medical treatment fails: intractable high-output heart failure, intractable portal hypertension, ischemic cholangitis (B2). Propose Bevacizumab in older patients or in patients in whom liver transplantation cannot be performed due to the severity of HHT complications (B2).
10. Provide information on patient associations as early as possible. Refer patients to social support initiatives and possibilities as appropriate (C2).

Disclosure of interest

The authors declare that they have no competing interest.

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