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Current guidelines for diagnosis and management of hepatic involvement in hereditary hemorrhagic teleangiectasia

Ielasi L *et al*. Liver involvement in hemorrhagic hereditary teleangiectasia

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Abstract

Hereditary hemorrhagic teleangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is the most common cause of hepatic vascular malformations in adults. Different vascular shunts (arteriovenous, arterioportal or portovenous) lead to different clinical manifestations. Even though no hepatic-related symptoms are reported in the majority of cases, the severity of liver disease could lead to refractory medical conditions, in some cases requiring liver transplantation.

The aim of this manuscript is to provide an updated overview of the current evidence regarding the diagnosis and treatment of HHT liver involvement and liver-related complications.

Core Tip: Hereditary hemorrhagic teleangiectasia (HHT) is the most common cause of hepatic vascular malformation in adults. Although liver involvement is common in HHT, most patients do not present any hepatic-related symptoms. Unfortunately, some patients have severe forms of disease with refractory medical conditions related to the hepatic vascular malformations. For those patients the only definitive treatment available at present is liver transplantation.

INTRODUCTION

Hereditary hemorrhagic teleangiectasia (HHT) or Rendu-Osler-Weber syndrome is a rare autosomal dominant disorder characterized by mucocutaneous teleangiectases and systemic vascular malformations (VMs). HHT can be ruled in by using the Curaçao criteria (recurrent epistaxis, multiple mucosal/cutaneous teleangiectases, visceral VMs and first-degree relative with HHT); if at least 3 of these criteria are met, the diagnosis of HHT is considered to be definite (Table 1)[1,2].

Molecular genetic test is useful in order to detect gene mutations. Endoglin (ENG, on chromosome 9) and activin A receptor type II-like 1 (ACVRL1, on chromosome 12) genes are involved in approximately 90% of cases and are responsible of HHT1 and HHT2, respectively. In addition to these two genes, mutation of SMAD4 has been identified in patients with the association of juvenile polyposis and HHT (PJ-HHT syndrome, approximately 2% of cases) in which anemia is the predominant symptom due to gastrointestinal bleeding. Mutations of GDF2 and RASA-1 genes have also been described but they are extremely rare (Table 2)[3,4].

Loss of function mutations in ENG and ACVRL1 cause anomalous angiogenesis leading to VMs development[2]. One of the primary mechanisms underlying aberrant vascular endothelial growth factor (VEGF)-related angiogenesis in HHT patients appears to be the overactivation of phosphatidylinositol 3-kinase (PI3K) signaling in endothelial cells[5]. High VEGF levels drive VMs development in mouse models and its normalization suppresses progression of these anomalous vascular structures[6,7].

HHT1 is more frequent in Mediterranean countries and it is characterized by a higher incidence of pulmonary and brain VMs, while HHT2 is more frequent in Northern Europe and North America with a higher incidence of hepatic VMs[8]. No significant difference was found in age at debut of symptoms and the severity of epistaxis between patients with HHT1 and HHT2. On the other hand gastrointestinal bleeding was reported to be more common in patients with HHT1[9]. HHT2 is associated to a higher risk of symptomatic liver disease[10].

HHT represents the most common cause of congenital hepatic vascular malformations in adults, and liver involvement is a commonly observed feature in the disease (Table 2)[11-13]; the mean age at diagnosis is 48 years[14].

Whilst more than 90% of cases do not present any hepatic-related symptoms, patients affected by HHT are susceptible to developing a range of clinical condition with varying presentations depending on the type of hepatic VM[15]. In some cases, the severity of clinical conditions requires liver transplantation. Women seems to have a more frequent (female prevalence 4.5 fold higher than males) and more severe liver involvement in both HHT1 and HHT2[16].

In the following paragraphs we will discuss the diagnostic and therapeutic approach for liver involvement in HHT patients.

HEPATIC VMS CLASSIFICATION AND CLINICAL MANIFESTATIONS

Three types of hepatic VMs have been described based on liver vascular anatomy: arteriovenous (the most frequent, between hepatic artery and hepatic vein), arterioportal (between hepatic artery and portal vein) and portovenous (between portal vein and hepatic vein)[15]. These different subtypes of hepatic vascular shunting usually coexist and affect the liver diffusely[17]. HHT liver involvement is a continuous process from small teleangiectases to very large VMs; size change during follow up has been observed in 21% of patients[10].

Arteriovenous shunts could cause high output cardiac failure (HOCF), ischemic cholangitis and mesenteric ischemia. Arterioportal shunts could cause portal

hypertension, but also biliary ischemia. Portovenous shunts could cause HOCF, but also portosystemic encephalopathy[15]. Generally, one of them predominates functionally, but fluctuation from a clinical condition to another is common.

HOCF is the most common complication of HHT liver involvement and it generally starts being clinically significant when intrahepatic shunt output is > 20% of cardiac output[18]. HOCF is associated to an increased risk of atrial fibrillation and the associated increased pulmonary blood flow secondary to liver VMs may lead to the development of post-capillary pulmonary arterial hypertension. Less frequently, HHT patients may develop a pre-capillary pulmonary arterial hypertension that seems to be related to the remodeling of small pulmonary arteries caused by ENG and ACVRL1 gene mutations with histologic features broadly similar to those observed in idiopathic pulmonary arterial hypertension. Right heart catheterization is essential to differentiate between the two forms[19].

Arteriovenous shunting can cause a blood steal with secondary bile ducts ischemia; this phenomenon is facilitated by the vascular anatomy of the biliary system, which derives its blood supply solely from the hepatic artery *via* the peribiliary plexus. Biliary ischemia can subsequently evolve in biliary strictures and dilations (secondary sclerosing cholangitis), secondary infection of the biliary system (infectious cholangitis), bilomas or biliary cysts (mimicking Caroli's disease), and elevation of serum alkaline phosphatase and gamma glutamyl transpeptidase. In the more severe forms, ischemia also affects hepatocytes causing hepatocellular necrosis leading to hepatic hemorrhage and bile leak[18,20].

Modification of normal liver perfusion may increase hepatocytes regenerative activity leading to development of focal nodular hyperplasia (FNH), 100 times more frequent in HHT patients than in general population, or nodular regenerative hyperplasia (NRH). In NRH the liver parenchyma undergoes a diffuse transformation into multiple regenerative nodules with hepatocytes arranged in plates, without fibrosis separating nodules.

Therefore, portal hypertension in HHT patients may be pre-hepatic, due to the increased blood flow from arterioportal VMs, or pre-sinusoidal, due to NRH (a well-known cause of non-cirrhotic intrahepatic portal hypertension).

Hepatocellular regeneration nodules may be associated with minimal perisinusoidal and portal fibrosis which can mimic cirrhosis on imaging and lead to being diagnosed incorrectly[18,21].

This appearance is commonly defined "pseudocirrhosis" since there is no significant liver fibrosis, liver function tests are generally normal and the risk of hepatocellular carcinoma is not as increased as for liver cirrhosis[22].

Xu *et al*[23] reported that hepatic involvement in HHT and Budd-Chiari syndrome (BCS) may be linked, suggesting a shared pathogenetic mechanism characterized by vascular dysplasia and a trombophilic condition induced by HHT that would eventually lead to BCS[24]. Nonetheless further studies are needed to evaluate the possible relationship between these two diseases.

Several disease progression predictors have been identified. Singh *et al*[25] proposed a clinical scoring system for the estimation of the probability of clinically significant liver disease in HHT patients. This score uses readily available information such as patient gender, age, hemoglobin and alkaline phosphatase at presentation, but is currently not widely recognized and still need to be validated (Table 3).

IMAGING SCREENING AND STADIATION

Screening for liver VMs should be offered to adults with a definite or suspected diagnosis of HHT[26] and the imaging test of choice for screening is Doppler ultrasound[27] for its accuracy in detecting hepatic VMs[28], its availability, repeatability, low cost and interobserver agreement[29-31]. In addition, Doppler ultrasound allows to establish the grade of severity of liver involvement and therefore correlates with patient outcomes and predictors of clinical outcomes[27].

Regarding the follow-up of hepatic VMs there are no standardized protocols nor consensus; ultrasound is usually repeated every 1 or 2 years according to the severity of liver involvement and is generally determined case by case.

Caselitz *et al*[28] defined major and minor criteria required for the diagnosis of liver VMs in HHT by Doppler ultrasound: a dilated common hepatic artery (> 7 mm) and intrahepatic arterial hypervascularization are the two major criteria; minor criteria are either Vmax in hepatic artery > 110 cm/s, low resistivity index (RI) of the proper hepatic artery (*i.e.* < 0.60), Vmax of portal vein > 25 cm/s and/or a tortuous course of extrahepatic hepatic artery. Presence of liver VMs in HHT is defined by two major criteria or one major criterion and two minor criteria[28]. According to Buscarini *et al*[27] severity grading ranges from 0.5 to 4 (Table 4)[32].

Hepatic artery dilation > 4 mm is a very sensitive parameter to differentiate HHT patients with or without liver involvement from the very early stages (Figure 1A)[32]; despite cirrhosis and hypervascular liver tumors may cause a dilation of hepatic artery, this rarely exceeds the upper normal limit as in HHT patients.

Peripheral subcapsular spots (identified by color Doppler) with high-velocity arterial blood flow and low RI are suggestive of small peripheral VMs, which are usually found from early stage in HHT patients with liver involvement (Figure 1B)[27].

Common hepatic artery dilation is also a predictor of HOCF development in patients with liver VMs[33]. A high velocity flow with low RI in intrahepatic branches of hepatic artery is highly suggestive of intrahepatic arterioportal shunt; furthermore, hepatic artery to portal vein shunts commonly cause pulsatility of portal flow with phasic or continuous reversal (Figure 1C). Arteriovenous shunts, on the other hand, usually result in a change in the Doppler waveform of hepatic veins (from triphasic to biphasic or even continuous patterns in severe involvements)[27,32].

FNH is common in HHT patients with liver involvement, and it generally appears as an isoechoic nodular lesion in liver parenchyma.

In those cases where the liver involvement is more severe, common findings are nodular and irregular liver surface with a coarse echo-pattern, previously known as pseudocirrhosis[34], as well as portal vein and hepatic vein dilation[27,32].

Multiphase contrast-enhanced abdominal computed tomography (CT) has an excellent yield and accuracy in defining liver vascular malformations and it is easily reproducible across different centers (Figure 2), however, it does not correlate with liver VMs severity and clinical presentations and is therefore recommended only if the expertise in detecting liver VMs using Doppler US is unavailable[17,35]. Nonetheless, it is widely used in complicated liver vascular malformation which are considered for liver transplantation[14] as it has the advantage of great accuracy in detecting biliary complications (*i.e.* necrotizing cholangitis with formation of bilomas)[32]; it is able to characterize the complexity of hepatic vascular alterations, the different types of shunts and parenchymal perfusion disorders[36,37] and it has great accuracy in differentiation between FNH from regenerative nodules[38].

Magnetic resonance imaging (MRI) of the liver shows great accuracy in characterizing focal liver lesions and in detecting liver VMs (they are better depicted on MRI angiograms and dynamic MRI images outlining a map of anomalous vessels)[39]. MRI is as accurate as multirow CT scan, with the advantage of the absence of ionizing radiations; nonetheless due its high cost and low availability it is recommended for diagnosis and follow-up of liver AVMs only when expertise in Doppler US is lacking[26,36].

The role of contrast-enhanced ultrasound (CEUS) with sulfur hexafluoride-filled microbubbles has been recently investigated in a cohort of 18 patients with HHT regarding macro and micro-circulation showing a higher percentage of hepatic VMs (especially of arterioportal shunts) than what is reported in literature[40]. However, CEUS seems to add no further information to Doppler US evaluation that still has great accuracy and sensitivity. It should also be noted that the use of sulfur hexafluoride-filled microbubbles is contraindicated in patients with right-to-left shunts and may

result in an unjustified risk considering the high percentage of pulmonary VMs in HHT patients[32].

Liver biopsy is generally not necessary for diagnosis of hepatic VMs due to the increased bleeding risk related to a percutaneous procedure. Therefore, hepatic nodules in HHT patients should be characterized non-invasively when possible. If a biopsy is needed, always consider the increased risk of bleeding in HHT patients[14,26].

LIVER TRANSPLANTATION

The first case of liver transplantation (LT) for HHT was reported in 1995[41]. Nowadays, LT is the recommended surgical option for severe hepatic involvement in HHT patients[26]. The main indication for LT are refractory HOCF and ischemic cholangitis (67.5% and 39.7% of cases, respectively)[42].

A recent systematic review by Riera-Mestre *et al*[42], reported 83 cases of LT for HHT worldwide. Perioperative complications within 30 days were described in 33.7% of patients (mainly bleeding complications) and a survival rate of 88% at six years has been reported.

While ischemic cholangitis is considered an urgent indication to LT, the best timing for transplantation in a patient with HOCF has not been defined yet.

MELD score was designed for cirrhotic patients and is widely used in defining the LT waitlist priority; HHT patients are exempt from being scored and should be included and prioritized in LT waitlist regardless of MELD score[43]. Right heart catheterization should always be performed in patients with HHT being evaluated for LT, to exclude severe pulmonary hypertension; LT can be undertaken if pulmonary vascular resistance is < 240 dynes· sec· cm^{-5} (< 3 Woods units)[14].

LT for HHT patients constitutes a more complex surgical procedure compared to other indications for LT and is characterized by higher blood transfusion requirement and more perioperative complications.

The hepatic artery in HHT patients may be dilated, tortuous and/or aneurysmatic and arterial graft anastomosis could be more challenging. Moreover, there is a high

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incidence of hepatic artery thrombosis after LT (about 7% of cases) that could result in need for re-transplantation. The presence of high-flow extrahepatic arterial teleangiectases may cause an arterial steal, so an attentive stadiation of disease before transplantation and an intraoperatively ultrasound arterial flow measurement through the anastomosis are strongly suggested[42,44].

The hyperdynamic state following recipient hepatic artery dissection constitutes is a potential risk of bleeding in any extrahepatic site of VMs. Fatal pulmonary bleeding has been described in two patients, so embolization of pulmonary VMs should be considered before LT[45,46].

Intrahepatic relapse of HHT lesions is a late but common event after LT. The median recurrence time is 127 mo and can occur up to 19 years after LT; the estimated cumulative risk of recurrence at 5, 10, 15 and 20 years is 0%, 16.7%, 47.9% and 87%, respectively[42,47–49]. For this reason, these patients require a life-long follow-up.

The pathophysiology of recurrence in the transplanted liver is still unclear. Presence of endothelial cells of recipient origin in the transplanted liver has been recently described[48]. Microchimerism after LT is a well-known phenomenon, but in this case the liver graft repopulation by patient endothelial cells may lead to an aberrant angiogenesis causing the recurrence of the disease[50].

An mTOR inhibitor-based immunosuppressive regimen after LT may reduce hepatic VMs recurrence by blocking the PI3K signaling pathway[51].

ENDOVASCULAR AND SURGICAL TREATMENTS

Hepatic VMs are generally considered not suitable for endovascular or surgical approach due to the high morbidity and mortality rates.

Transarterial embolization is generally used for treating HOCF and portal hypertension. This procedure is performed in multiple stages (one to five sessions); among the several protocols proposed, the most used one consists in an initial embolization of vascular bed with a mixture of polyvinyl alcohol followed by

embolization with microcoils. Arterial branches of right and left lobe have to be embolized in different sessions[52].

A peri-procedural infusion of analgesics, anti-emetics and steroids is generally advised; some authors also consider a peri- and post-procedural prophylactic antibiotic coverage[53].

The most common complications are biliary or hepatic necrosis that occur in 20%-60% of cases[53]; need for emergent LT and death is reported in up to 10% of cases[54].

Regarding the high risk of ischemic hepatic damage, transarterial embolization is generally contraindicated in patients with signs of biliary involvement[14].

There have been very few published accounts of transjugular intrahepatic portosystemic shunt (TIPS) as portal decompressive intervention. The high risk of worsening the cardiac output and the high bleeding risk related to the puncture lead to consider this treatment largely unsuccessful and so not recommended[55,56].

Hepatic artery banding and/or ligation are other potential approaches for managing HOCF due to hepatic VMs. Banding consists in the diameter reduction by one third to a half of the pre-operative diameter of common hepatic artery and potentially lobar arteries; ligation consists in closure of feeding arteries of the lobe predominantly involved by VMs.

The diameter reduction achieved with arterial banding should be sufficient to reduce liver hyperperfusion, without causing ischemic hepatobiliary damage. Banding should be guided by colorDoppler ultrasound with a desired hepatic artery flow of 330 ± 80 mL/min[57]; another indirect parameter of sufficient arterial banding is the return of arterialized areas of liver surface to normal red color[58].

CT angiography is always recommended before surgery in order to investigate extra-hepatic vascular anatomy. If appropriate, collateral circulation arising from superior mesenteric or left gastric arteries could also be ligated and enlarged gastroduodenal artery banding may also be considered[58].

Based on the risk of hepatic necrosis, these procedures are contraindicated in case of significant portovenous shunting[59].

For a long time, hepatic artery ligation or banding has been used in limited number of cases due to the high rate of ischemic cholangitis and undefined long-term survival[57,60,61]. Lui *et al*[58] recently reported a series of 13 patients treated with hepatic artery ligation/banding with a low rate of peri- and post-operative complications (only two patients experienced cholangitis, who were treated conservatively), improvement of symptoms and good survival outcome (only one patient died in a median follow-up of 50 mo). Authors advise against dissecting malformed and tortuous vessels around extrahepatic biliary tract in order to reduce the risk of ischemic damage and against dividing perihepatic ligaments in order to preserve arterial flow to the liver.

Conventional hepatic surgery, like segmental resection or hemi-hepatectomy, is anecdotal[62] or reported for hepatic shunting in non-HHT patients[63] and for non VM indications in HHT patients[64,65]. This approach could be considered in very selected patients with symptomatic disease and very large VMs localized in a single segment/Lobe, but such kind of indication should be given with caution.

Considering the high complication and mortality rates, together with their palliative role, endovascular and surgical treatments are still generally not recommended and should be proposed only in severely symptomatic patients that are not transplant candidates and have failed medical therapy; these approaches should be deliberated by a multidisciplinary team and should be performed only by expert physicians in referral centers[14].

MEDICAL TREATMENTS

First-line medical treatment, such as management of anemia with iron replacement therapy or management of mild bleedings with antifibrinolytics, concerns almost all HHT patients but it is not the aim of this paper, so it will not be discussed further. At the same time, first-line medical treatment for hepatic VM-related HOCF should be evaluated managed by physicians with expertise in that field (such as cardiologists) and it goes beyond the purpose of this paper.

Management of portal hypertension follows the same principles as in patients without HHT[66,67], but non-selective beta-blockers should be used with caution in patients with HOCF, although they still are the drugs of choice[26].

Similarly, the management of portosystemic encephalopathy follows the same principles as in cirrhotic patients without HHT (*i.e.* lactulose and rifaximin)[26,68].

Infectious complications, such as cholangitis and hepatic abscesses, generally require antibiotic therapy. Large biliary duct obstruction is uncommon in HHT patients, and endoscopic retrograde cholangiopancreatography with stenting is not indicated[26], because it seems to increase the risk of infection in ischemic ducts and the risk of hemobilia[69,70].

Over the last few decades, research has primarily focused on utilizing antiangiogenetic drugs with the aim of targeting the aberrant angiogenesis causing VM formation and endothelial frailty. Several molecules have been investigated and multiple clinical trials are ongoing (such as thalidomide[71,72], tacrolimus[73], sorafenib[74], pazopanib[75,76], doxycycline[77,78] and others) with interesting results on nasal and gastrointestinal bleeding control, but the only molecule that has been studied for HOCF related to hepatic VMs is bevacizumab.

Bevacizumab is a humanized monoclonal antibody which exerts its antiangiogenic activity by inhibiting the VEGF. In 2012, its efficacy has been prospectively investigated in HHT patients with HOCF related to liver VMs resulting in a decrease cardiac output[79]; a reduced or delayed need for transplantation has also been described[80]. Bevacizumab has also demonstrated a reduction in nasal and gastrointestinal bleedings resulting in an improvement of anemia, decrease of blood transfusion need and better quality of life[81,82].

Numerous dosing schedules have been investigated, but the most common dose for initiation was 5 mg/kg every 2 wk for a total of 6 injections; infusion duration should be of at least 30 min (first administration should be given in at least 60 min to assess patient drug tolerance)[79]. Despite a high inter-patient bleeding-free interval, almost all patients relapse after a year of discontinuation of bevacizumab and they may

require maintenance therapy or may repeat a new administration cycle that could become lifelong[83]. To date, there are no prospective studies concerning maintenance therapy; the dosing schedule should therefore be determined based on patient response and tolerance[81,83].

Similarly, the safety of ~~for~~ long-term bevacizumab administration has not been prospectively evaluated. However, it could be inferred indirectly from prolonged administration of the drug for other indication.

The most frequent adverse events are generally mild and infusion-related, such as headache, nausea and vomiting, asthenia, abdominal pain, muscle pain, diarrhea and rash[79].

A major concern among drug-related adverse events is addressed to arterial hypertension, venous thrombosis and hemoptysis from pulmonary VMs[81,84]. Therefore, it is crucial to assess patients prothrombotic conditions prior to starting therapy with bevacizumab, and pulmonary VMs screening and treatment should be performed according to guidelines as for every HHT patient. Other potentially serious adverse events are gastrointestinal perforation and proteinuria[84]. Since a delay in wound healing has been reported during antiangiogenetic treatment, it is recommended to stop bevacizumab 6-8 wk before surgery and to restart it only if wounds are totally healed.

Bevacizumab is contraindicated in patients with severe arteriopathy, a history of ischemic complications, recent deep vein thrombosis (< 6 mo) or recent severe infection (< 1 mo) and should be used with caution in patients with non-post-capillary pulmonary hypertension[85]. It is also contraindicated in pregnancy, so effective contraceptive measures should be adopted by women in childbearing age during treatment and for six months after discontinuation[85].

A recent international expert consensus paper suggests a monitoring protocol for HHT patients treated with bevacizumab which consists in regular clinical examination (blood pressure measurement, epistaxis monitoring, blood transfusion require recording, adverse events collection) laboratory (blood cell count, liver and kidney

function, ferritin, proteinuria) and scheduled echocardiography with cardiac index measurement[85].

To date, there is not sufficient available evidence from randomized control trials and bevacizumab is not market-authorized for HHT, but international expert consensus recommends considering intravenous bevacizumab for severe and refractory nasal and/or gastrointestinal bleeding and for HOCF secondary to hepatic VMs not sufficiently responder to first-line medical therapy[26,85,86]. Based on the rates of minimal or partial response to bevacizumab and the recurrence after drug discontinuation, intravenous bevacizumab should be considered as a potential "bridge" therapy to LT.

CONCLUSION

Liver involvement is very common in HHT patients and hepatologists should be aware of this condition and the available diagnostic and prognostic tools. Fortunately, clinically significant liver disease is uncommon, but its management could be challenging. Liver transplantation remains the only curative treatment for these patients. Endovascular and surgical approaches should be avoided in patients with liver VMs. Bevacizumab has shown promising results, but it should be used with caution and only in referral centers.

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