Hepatic involvement in hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler Weber syndrome

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Abstract

Background and study aims : **Hepatic involvement in hereditary hemorrhagic telangiectasia (HHT) is usually asymptomatic and does not require treatment. However, when present, clinical manifestations can cause considerable morbidity and mortality. Current expertise in the variable clinical manifestations and recommendations for diagnostic approach and management of hepatic involvement in HHT are outlined.**

Methods and materials : **A review of current literature was performed using the MEDLINE search string : "Hereditary hemorrhagic telangiectasia [ALL] OR Rendu-Osler-Weber [ALL] AND (liver OR hepatic [ALL])".**

Results : **Due to the lack of therapeutic consequence, systematic screening for hepatic involvement in asymptomatic patients with HHT is currently not recommended. In symptomatic patients, diagnostic tools include non-invasive techniques such as abdominal color Doppler ultrasound, CT and/or MRI. In any case, liver biopsy should be avoided in patients with suspected HHT because of the high bleeding risk.**

Liver transplantation is currently the only curative option for symptomatic hepatic involvement in HHT. Except for biliary or hepatocellular necrosis, which require urgent liver transplantation, consensus on the most appropriate timing of transplantation is lacking. Recent studies have shown a promising role for angiogenesis inhibitors as a causative treatment for hepatic involvement in HHT and its complications.

Conclusions : **Identification of specific risk factors for progression to the symptomatic phase is one of the main future challenges. This would subsequently allow for individualized and cost-effective screening of high-risk patients when they are still in the asymptomatic stage. However, until then screening in asymptomatic patients is not recommended. Additionally the effect of preventive measures in this high-risk population on the development of symptomatic liver involvement and on poor outcome should be established.** (Acta gastroenterol. belg., **2015**, 78, **319-326**).

Key words : hereditary hemorrhagic telangiectasia, Rendu-Osler-Weber, hepatic, liver.

Background

Hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome is an autosomal dominant disorder with age-dependent penetrance (1). It is characterized by vascular malformations (VMs), ranging from small telangiectasias to large visceral VMs. Clinical manifestations range from asymptomatic to life-threatening complications, depending on the number and locations of these VMs. The combination of epistaxis, gastrointestinal bleeding and mucocutaneous telangiectasias is typically described (2,3). However, visceral VMs can present anywhere in the vascular system, most commonly pulmonary (> 50%), hepatic (30%) and cerebral (10%) (4).

This review will focus on the clinical manifestations, complications, diagnostic approach and management of hepatic involvement in HHT.

Clinical diagnostic criteria for HHT, known as the Curaçao citeria, were established in 2000 (Table 1) (5). If three or more criteria are present, a diagnosis of HHT diagnosis is considered 'definite'. HHT is suspected or 'possible' if two criteria are present and 'unlikely' if only one criterion is present.

Most patients have a heterozygous mutation in one of two disease-related genes both involved in the transforming growth factor-β (TGF-β) pathway. Patients with HHT type 1 have a mutation in the endoglin (ENG) or HHT1 gene. This genotype correlates with an earlier onset of epistaxis and with more frequent and more symptomatic pulmonary VMs and brain abscesses (6,7). Hereditary hemorrhagic telangiectasia type 2 involves a mutation in activin A receptor type-II like (ACVRL1 or ALK-1) or HHT2 gene. Liver involvement is more frequently associated with mutations in the ACVRL1 or HHT2 gene and subsequently more prevalent in patients with HHT type 2 (8). Evidence of a not yet identified HHT3 gene exists, causing a classical HHT phenotype with pulmonary involvement (9).

Additionally, mutations in the SMAD4 (mothers against decapentaplegic-related proteins family member 4) gene have been described causing a rare syndrome which combines HHT and juvenile polyposis (HHT/JP syndrome) (10).

Methods

A review of current literature was performed using the MEDLINE search string : "Hereditary hemorrhagic telangiectasia [ALL] OR Rendu-Osler- Weber [ALL] AND (liver OR hepatic [ALL])". Articles were selected based on relevancy of the abstract, full text availability and

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Table 1. — **Curaçao clinical diagnostic criteria for HHT**

Criteria	Description
Epistaxis	Spontaneous, recurrent nose bleeds
Telangiectasias	Multiple at characteristics sites (lips, oral cavity, fingers, nose)
Visceral lesions	Pulmonary, hepatic, cerebral, spinal, gastrointestinal VMs (with or without bleeding)
Family history	A first degree relative with HHT according to these criteria

Definite : ≥ 3 criteria. Possible : 2 criteria. Unlikely : 1 criterion.

publication date. Related citations were reviewed and retained if they contained additional information.

Results

Pathophysiology and clinical manifestations

Hepatic involvement is found in up to 75% of patients with HHT. However, only a small percentage (5-8%) exhibit symptomatic liver disease (11). Liver involvement involves a large spectrum of intrahepatic shunting, ranging from small telangiectasias to large vascular malformations. Three types of intrahepatic shunting have been described : arterioportal (hepatic artery to portal vein), arteriosystemic (hepatic artery to hepatic vein) and portosystemic (portal vein to hepatic or systemic veins) (11). All three types can co-exist, however usually one type predominates clinically.

Clinical manifestations of symptomatic liver involvement in HHT include high-output heart failure, portal hypertension and biliary disease, depending on the predominant type of shunt (12). Almost all patients with high-output heart failure, the most frequent and sometimes presenting manifestation, have arteriosystemic shunts and/or portosystemic shunts (12). Chronically increased preload and cardiac output causes a hyperdynamic circulatory state and congestive heart failure. Symptoms include exertional dyspnea, orthopnea, ascites and edema. Secondary pulmonary hypertension and atrial fibrillation may occur (13).

Portal hypertension in HHT is due to direct arterioportal shunting or can be secondary to nodular regenerative hyperplasia (NRH) with regenerative nodules compressing the sinusoids and central lobular venules (12). Clinical presentation includes ascites, esophageal varices and variceal hemorrhage. Gastro-intestinal bleeding is also more frequent in patients with portal hypertension (12). However, GI bleeding is mostly caused by upper GI telangiectasias and also occurs in the absence of portal hypertension (13).

Diffuse or focal increased blood supply due to VMs increases hepatic regenerative activity and thus predisposes to the formation of both nodular regenerative hyperplasia (NRH) and focal nodular hyperplasia (FNH) (14). Nodular regenerative hyperplasia is characterized by the presence of several regenerative nodules smaller than 3 cm, causing nodular appearance of the liver surface (15). In the past, nodular transformation in HHT was frequently misdiagnosed as “cirrhosis hepatic telangiectasia” or “atypical cirrhosis”, especially in the presence of portal hypertension. However, NRH can be distinguished from true cirrhosis by the preservation of normal hepatocellular architecture in the nodules and by the absence of fibrous septa between the nodules (15). If cirrhosis is present in patients with HHT, it is mostly due to chronic viral infection as a complication of blood transfusions for anemia.

Focal nodular hyperplasia is defined as a benign pseudotumor, histologically characterized by a central anomalous artery causing proliferation of surrounding normal hepatocytes, Kupffer cells and fibrous septa (14,16). Together this forms a central stellar fibrotic scar. Patients are usually asymptomatic and have normal liver function tests. In less than one third of patients, epigastric or right upper quadrant pain is found (17). There is no definite evidence the FNH can lead to malignant transformation.

Furthermore, as the biliary tree is exclusively vascularized by the hepatic artery, arteriosystemic or arterioportal shunting may lead to ischemia of biliary tree by steal syndrome. This in turn leads to chronic cholestasis, bile cysts or strictures with or without acute cholangitis. Infrequently, severe biliary ischemia causes necrotizing cholangitis with hepatocellular necrosis, a process called “acute hepatic disintegration” (18). Clinically it is characterized by right upper quadrant pain, jaundice, fever and sepsis.

Other, less frequent clinical manifestations include hepatic encephalopathy due to portosystemic shunts and abdominal angina due to a mesenteric arterial steal syndrome (19).

Screening and diagnosis

General agreement exists on screening for pulmonary VMs, as pre-symptomatic treatment can help prevent life-threatening complications (20). Guidelines for initial evaluation and follow-up of patients with suspected HHT are outlined in table 2 (21,22). In general, screening consists of basic clinical examination, laboratory evaluation for anemia and iron deficiency, screening for pulmonary and, in some cases, cerebral VMs (21).

Less consensus exists on the role of screening for hepatic VMs in asymptomatic HHT patients, because treatment is not recommended in these patients (13,23). Exceptions can be made in patients with a suspected

Table 2. — **Guidelines for initial evaluation and follow-up of patients with (suspected) HHT**

Assessment	Initial evaluation	Further evaluation
Pulmonary VMs : *Transthoracic contrast echocardiography (TTCE)*	At diagnosis	– Negative screening : repeat TTCE every 5-10 years or after pregnancy or puberty – Positive TTCE : Chest CT – Small, untreated PAVMs : asses individually, chest CT every 1-5 years – After embolization of PAVMs : chest CT within 6-12 months, then every 3 years
Gastrointestinal VMs : *Full blood count, iron status*	At diagnosis	– Yearly in those ≥ 35 years of age – If anemia disproportionate to epistaxis : upper endoscopy and colonoscopy
Cerebral VMs : *Cranial MRI*	If definite of possible diagnosis according to the Curaçao criteria	– Negative screening : do not repeat
Hepatic VMs : *Color Doppler ultrasound*	If 1-2 criteria according to the Curaçao criteria and inconclusive/unavailable genetic testing OR According to clinical risk stratification ?* – Low : no screening – Intermediate <40% : no screening – Intermediate 40%-80% : at diagnosis – High : at diagnosis	Clinical risk stratification ?* – Low : reconsider screening every 3-5 years – Intermediate < 40% : reconsider screening every 2 years – Confirmed hepatic VMs : serial liver enzymes and hemoglobin every 6 months, TTCE annually

*As proposed by Singh *et al*. in "Identifying the presence of clinically significant hepatic involvement in hereditary haemorrhagic telangiectasia using a simple clinical scoring index", 2014, Journal of Hepatology, 61 (1) : 124-131 (25).

Note. Summary of recommendations for surveillance in HHT. Adapted from "Hereditary haemorrhagic telangiectasia, an Australian cohort : clinical and investigative features" by Salaria M., Taylor J., Bogwitz M. *et al*., 2014, Internal medicine journal, 44 (7) : 639-644 (22).

diagnosis according to the Curaçao criteria, to confirm the diagnosis (24). In patients fulfilling 1 or 2 diagnostic criteria and in whom genetic testing is unavailable or inconclusive, screening for hepatic VMs is recommended.

Considerable differences in cumulative 5-year survival between patients with asymptomatic (91.6%) and symptomatic (70.8%) hepatic involvement have been described (25).

As a future target, identification of specific risk factors for progression to the symptomatic stage, could allow for identification and subsequent screening when these high-risk patients are still in the asymptomatic stage. The clinical penetrance of HHT is age-dependent and, in particular hepatic VMs were found only to occur around the age of 50 (1,6,13). Retrospective analysis of case series have also found a higher prevalence of liver involvement in women, with a higher rate of symptomatic disease and more need for liver transplantation (19,26). Furthermore, symptomatic hepatic involvement was found only to occur in patients with ACVRL1 mutations, associated with HHT type 2 (6,25). Consistent with these findings, the combination of an ACVRL1 mutation and abnormal liver biology was found to be predictive for hepatic involvement on color Doppler ultrasound (27). However, routine genetic testing is not always available.

Recently, a clinical scoring index, based on age, gender and hemoglobin and alkaline phosphatase level at presentation, for the identification of patients with clinically significant liver disease has been developed (Table 3) (25). Using this clinical risk stratification, patients at low (< 5% probability) or high risk (> 80% probability) for harboring clinically significant liver disease were identified. In patients identified with a high-risk score, confirmation of hepatic VMs is recommended (Table 2) (25). For patients with intermediate scores, the scoring index was less accurate in distinguishing clinically significant from non-significant liver disease. More accurate risk stratification for patients with an intermediate risk may be accomplished by using the full logistic regression model as calculated by Sigh *et al*. (25). If the subsequently calculated probability of clinically significant liver disease is less than 40%, screening is not recommended. If the calculated risk ranges from 40 to 80%, screening is recommended.

Furthermore, prospective evaluation of hepatic involvement in asymptomatic patients with HHT found a significant correlation between both the diameter of the main hepatic artery and presence of FNH and high cardiac output, a risk factor of high-output heart failure (27). However, long- term evaluation is needed to determine which portion of patients will eventually develop symptomatic high-output heart failure.

In patients with symptoms suggestive of hepatic VMs, it is important to establish a diagnosis. Early identification and treatment of complications due to hepatic VMs, such as high-output heart failure, has proven to have a significantly better outcome (13). In patients without a diagnosis of HHT presenting with symptoms of heart failure, portal hypertension and/or cholestasis, clinical suspicion is recommended (28). Further evaluation through personal and family history of epistaxis, telangiectasias, gastro-intestinal bleeding and cerebrovascular accidents is warranted.

Color Doppler ultrasound is commonly used as a first-line evaluation of hepatic involvement in patients with HHT (24,29). In 2003, major and minor sonographic criteria with high sensitivity and specificity have been proposed (Table 4). Major criteria were dilatation of the

Table 3. — **Clinical risk stratification for the development of symptomatic liver involvement ***

Clinical feature		Score
Age at presentation (years)	> 47	1
	≤ 47	0
Sex	Female	1
	Male	0
Hemoglobin level at presentation (G/DL)	< 8	3
	8-12	2
	12-16	1
	> 16	0
Alkaline phosphatase at presentation (IU/L)	> 300	4
	225-300	3
	150-224	2
	75-149	1
	< 75	0

* Clinical probability : 0-2 : Low. 3-6 : Intermediate. 7-8 : High.

Note. Simple Clinical Scoring Index to predict presence of clinically significant hepatic involvement in HHT. Adapted from "Identifying the presence of clinically significant hepatic involvement in hereditary haemorrhagic telangiectasia using a simple clinical scoring index" by Singh S. *et al*., 2014, Journal of Hepatology, 61 (1) : 124-131 (25).

common hepatic artery (> 7 mm) and intrahepatic arterial hypervascularisation (29). Increased peak velocity of the hepatic artery (> 110 cm/s) and portal vein (> 25 cm/s), hepatic artery resistive index < 0.6 and tortuous course of the extrahepatic hepatic artery are considered minor criteria. For the diagnosis of hepatic involvement in HHT, combination of both major criteria or one major criteria with at least 2 minor criteria is suggested (29). However, when setting the cut- off value for hepatic artery dilatation at > 6 mm subsequent studies found no overlap between normal subjects and patients with HHT (30).

Additionally, the detection of peripheral hypervascularisation was suggested to correlate with early stage microscopic VMs, before hepatic artery dilatation (30). In 2008, Buonamico *et al*. described a new color Doppler ultrasound sign with 95% sensitivity and 68% specificity for identifying hepatic VMs in HHT, termed the "color-spot" (31). This was defined as a subcapsular vascular spot due to the tortuous peripheral branches of the hepatic artery, with a high-velocity arterial blood flow and low resistivity index.

Increasing diameter of the main hepatic artery and presence of FNH on color Doppler ultrasound , both associated with arteriosystemic shunting, were found to correlate with a high cardiac index and risk of high-output heart failure (27).

Multidetector helical contrast-enhanced CT scan has a high sensitivity for detecting different intrahepatic shunts (11).

Arterioportal and arteriosystemic shunts are indirectly detected during the early arterial phase, by the early and prolonged enhancement of the hepatic and portal veins respectively (32). In theory, the less prevalent portosystemic shunts can be detected during the late arterial phase. However, it remains difficult to clearly distinguish the portal from a hepatic vein on contrast-enhanced CT scan (32).

Indirect signs of portal hypertension, such as a dilated portal vein, splenomegaly and gastro- esophageal varices can also be detected with CT scan. Other indirect signs of hepatic involvement include telangiectasias, large confluent vascular masses, biliary strictures, dilatations and cysts and perfusion defects.

Biliary involvement is more frequently found in symptomatic patients, suggesting that biliary ischemia correlates directly with the degree of shunting and thus develops later in the disease process (33).

Perfusion defects such as transient hepatic parenchymal enhancement are frequently associated with arterioportal shunts. Due to the diverted blood flow from the high-pressure hepatic artery into a low-pressure portal vein branch, hyperattenuation of the associated hepatic parenchyma during the early arterial phase occurs (32).

So far, the use of MRI for diagnosing hepatic involvement in HHT has been limited. Studies have shown that MRI and MR angiography (MRA) are also accurate in detecting hepatic VMs, perfusion defects and biliary tract disorders, without the need for ionizing radiation (34, 35). Additionally, it allows evaluation of complex vascular anatomy before interventional procedures (34).

Angiography is considered as the gold standard for diagnosing hepatic VMs. However, this invasive procedure is currently reserved for pre-transplantation work-up or before transarterial embolization. It remains the most preferred method for diagnosing a mesenteric arterial steal syndrome and portosystemic shunts.

A diagnosis made by a combination of non-invasive techniques such as abdominal color Doppler ultrasound, CT and/or MRI is currently recommended (17).

Table 4. — **Characteristic findings of hepatic involvement in HHT on color Doppler ultrasound, multislice CT, MRI and angiography**

Color Doppler Ultrasound	Major criteria
	Dilated common hepatic artery (> 6 mm)
	Intrahepatic arterial hypervascularisation
	Minor criteria
	Peak velocity of the hepatic artery > 110 cm/s
	Peak velocity of the portal vein > 25 cm/s
	Hepatic artery resistive index < 0.6
	Tortuous course of the extrahepatic hepatic artery
	Peripheral hypervascularisation
	Subcapsular color-spots with resistive index < 0.45
Multislice CT, MRI	Intrahepatic shunts : arterioportal and arteriosystemic
	Telangiectasias : round formations 5-7 mm
	Perfusion defects : peripheral and wedge-shaped hyperattenuated areas during the arterial phase
	Large confluent vascular masses > 10 mm, consistent of telangiectasias
	Portal hypertension : dilated portal vein (> 13 mm), splenomegaly (longitudinale diameter longitudinal > 130 mm) and gastro-esophageal varices
	Biliary strictures, dilatations and cysts
	NRH, FNH
Liver angiography	Intrahepatic shunts : arterioportal, arteriosystemic, portosystemic
	Mesenteric arterial steal syndrome

Because of the high bleeding risk due to hepatic VMs, percutaneous ultrasound-guided liver biopsy should be avoided in patients with suspected or proven HHT. Histology is fairly typical and involves abnormal ectatic vessels, biliary abnormalities, sinusoidal fibrosis and/or nodular hyperplasia (12) However, given the bleeding risk and characteristic findings on imaging, histology is considered unnecessary for the diagnosis of hepatic involvement in HHT (21).

Laboratory abnormalities are nonspecific and may include elevated alkaline phosphatase, gamma-glutamyl transferase levels and mild elevations of serum transaminase levels, suggesting anicteric cholestasis (26). Functional liver tests (e.g. prothrombin time, albumin) are usually normal.

Diagnostic work-up for hepatic nodules in HHT, suggestive of focal nodular hyperplasia should include non-invasive testing such as laboratory evaluation (including serological tumor markers) and imaging (24). Contrast-enhanced imaging (color Doppler ultrasound, CT or MRI) is accurate in differentiating FNH from malignant hepatic tumors. Focal nodular hyperplasia is characterized by a strong and homogenous contrast enhancement in the arterial phase, except for the central scar which remains hypo-attenuated (17, 36). In the portal venous phase the lesion becomes iso-attenuated to liver parenchyma. Central scar enhancement can be seen in the delayed phase. Contrarily, liver metastasis are generally hypovascular and appear hypo- or iso- attenuated on contrast-enhanced imaging (36). Hepatocellular carcinoma (HCC) presents with early arterial phase enhancement and a rapid wash out in the portal venous and delayed phase (36). Hepatic hemangiomas typically exhibit discontinuous, nodular, peripheral enhancement starting in the arterial phase, followed by gradual central filling in the portal venous phase (36). Invasive testing such as biopsy and excision is not recommended.

In patients with dyspnea and suspected high-output heart failure, bubble echocardiogram or transthoracic contrast echocardiography (TTCE) and subsequent right-heart catheterization can be performed to evaluate pulmonary artery pressure (37). In patients with arterioportal shunts and portal hypertension, upper endoscopy is recommended for the evaluation of esophageal varices (26).

Treatment

In asymptomatic patients, treatment is not recommended (24).

High-output heart failure is treated with salt and fluid restriction, correction of anemia and arrhythmias and conventional medical therapy such as diuretics, angiotensin-converting enzyme inhibitors, β-blockers and digoxin.

Management of portal hypertension in patients with HHT is identical to the management in cirrhotic patients, aimed at preventing and treating its complications. It consists of salt restriction, diuretics and abdominal paracentesis followed by albumin replacement. Active

variceal hemorrhage is treated with endoscopic banding or sclerotherapy. Secondary prophylaxis for bleeding from esophageal varices consists of nonselective β-blockers and/or endoscopic ligation. The use of pharmacological treatment in controlling gastrointestinal bleeding and preventing rebleeding is still unclear. It could be useful in refractory bleeding and lesions inaccessible on endoscopy (38). Hormone treatment (oestrogen, progestagen) has been successfully used in controlling epistaxis and gastrointestinal bleeding in patients with HHT, with few side effect (39). Octreotide has also been found effective in reducing blood loss from gastrointestinal bleeding and reducing the need for transfusion (38,40). However, all of these case series had a small sample size, larger randomized-controlled trials are needed to confirm these findings (38). Placement of a transjugular intrahepatic portosystemic shunt (TIPPS) is currently not recommended because it will increase shunting and worsen the hyperdynamic circulatory state and high-output heart failure (24).

Symptomatic biliary ischemia should be treated with analgesics. Acute cholangitis is treated with antibiotics. Endoscopic retrograde cholangiopancreatography (ERCP) should be avoided in patient with HHT because of the risk of ascending cholangitis (28).

Orthotopic liver transplantation is currently the only curative option for symptomatic hepatic involvement in HHT. It should however be reserved for patents who fail medical therapies. The main indications for liver transplantation are intractable high-output heart failure, intractable portal hypertension and/or severe biliary necrosis causing hepatic failure (19). Except for biliary or hepatocellular necrosis, which require urgent liver transplantation, consensus on the most appropriate timing of liver transplantation is lacking (24). Right heart catheterization should always be performed pre-transplantation to evaluate the presence of severe pulmonary hypertension, which is associated with high perioperative mortality (24). Liver transplantation in patients with secondary pulmonary hypertension should be performed before fixed hypertension occurs (41). Before liver transplantation, treatment of major pulmonary VMs is recommended to prevent brain abscesses. Mortality is highest peri- and postoperatively, ranging from 10 to 20%, mostly due to bleeding and cardiac failure (41). The 5-year survival rate was found to be approximately 80% (41). Post-transplantation an improvement in cardiovascular and pulmonary functions is seen, greatly improving quality of life (41).

Transarterial embolization and hepatic artery surgical ligation is currently not recommended as a first-line therapeutic option for hepatic involvement in HHT. Studies have shown an improvement in the mesenteric arterial steal syndrome and cardiac and pulmonary functions (42). However, in up to 30% of treated patients severe morbidity and mortality due to hepatocellular and/or biliary necrosis is described (19). In patients with arteriosystemic shunts, this may be due to deterioration of chronic biliary ischemia after embolization of the hepatic artery. In patient with portosystemic shunts, blood supply to the liver parenchyma is largely dependent of the hepatic artery (32). Embolization or ligation of the hepatic artery may lead to an insufficient vascularization and hepatocellular necrosis (12). Furthermore, effects are usually transient and data on long-term outcome is lacking. Transarterial embolization should therefore only be considered in patients not responding to medical treatment and who are not suitable for liver transplantation. Moreover, liver cirrhosis, severe biliary disease and/or portosystemic shunts should be ruled out.

Overexpression of vascular endothelial growth factor (VEGF) and transforming growth factor (TGF)-β1 have been suggested to play a role in the pathogenesis of HHT (43). Targeting this pathway could be a potential therapeutic target in HHT. Bevacizumab (Avastin®), a monoclonal antibody to VEGF, has been successfully used in controlling epistaxis in patients with HHT (44). Furthermore, several nonrandomized studies have found reduction in hepatic vascularization and partial or complete improvement of high-output heart failure and complications of portal hypertensions (e.g. ascites, hepatomegaly, esophageal varices) following the use of bevacizumab intravenously 5 mg/kg every 2 weeks for a total of 6 injections (45-48). However, after cessation of bevacizumab symptoms gradually reappeared after 9 months in one patient (47). Side effects observed include grade III hypertension (> 180/110 mmHg) and dose-dependent proteinuria (48). VEGF inhibition has also been implicated in renal thrombotic microangiopathy (49). Until more research is performed, it is recommended that bevacizumab should be reserved as bridging therapy for transplantation or for patients in whom liver transplantation is not feasible.

Discussion

Hepatic involvement, as opposed to pulmonary involvement in HHT is usually asymptomatic and presymptomatic treatment is not available. However if symptomatic, hepatic involvement is usually associated with substantial impact on quality of life and significant mortality.

Due to the lack of therapeutic consequence, systematic screening in asymptomatic patients is not recommended. Exceptions can be made to confirm the diagnosis of HHT according to the Curaçao criteria.

Identification of risk factors for progression to the symptomatic phase is one of the main future challenges, as this would allow for identification of these high-risk patients when they are still in the asymptomatic stage. Accurate identification of patients at high risk for developing clinically significant liver disease could subsequently allow for individualized and cost-effective screening. Only patients with an ACVRL1 mutation, associated with HHT type 2, were found to develop symptomatic liver disease. However, routing genetic

testing is not always available. The recently developed clinical risk stratification, based on age, gender, hemoglobin and alkaline phosphatase level, can be a useful tool for identifying patients with clinically significant liver disease, who may benefit from presymptomatic screening. More prospective studies are needed to validate this clinical score before it can be commonly used in practice. Moreover, currently this score has only been validated for the identification of patients harboring clinically significant liver disease in a presymptomatic stage, not for predicting the development of symptomatic liver disease in asymptomatic patients with hepatic VMs.

Another objective is to establish the effect of preventive measures in this high-risk population on the development of symptomatic liver involvement and on poor outcome. Moreover, more research is needed to identify and confirm specific risk factors for the development of high-output heart failure, portal hypertension or biliary ischemia.

In symptomatic patients, treatment is directed towards the specific clinical manifestation. As a last resort, orthotopic liver transplantation can be considered. Post-transplantation, a significant improvement in cardiovascular and pulmonary functions is seen and long-term survival rates are favorable. Except for biliary or hepatocellular necrosis, which require urgent liver transplantation, consensus on the most appropriate timing of liver transplantation is lacking. More data on the natural history of hepatic involvement in HHT through family screening and predictors of poor outcome is needed.

Recent studies have shown a promising role for angiogenesis inhibitors, such as bevacizumab, as a causative treatment for hepatic involvement in HHT and its complications. More prospective and randomized-controlled studies are needed to confirm these results, determine the appropriate dosing scheme, long-term effects and need for maintenance therapy.

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