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REVIEW ARTICLE

Hereditary hemorrhagic telangiectasia: from molecular biology to patient care

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Summary. Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular disorder characterized by severe and recurrent nosebleeds, mucocutaneous telangiectases, and, in some cases, life-threatening visceral arteriovenous malformations of various types, including pulmonary, hepatic, cerebral, and spinal. Gastrointestinal telangiectases are frequent and may cause severe bleeding. HHT type 1 results from mutations in *ENG* on chromosome 9 (coding for endoglin), and HHT type 2 results from mutations in *ACVRL1* on chromosome 12 (coding for activin receptor-like kinase 1). Mutations of either of these two genes account for most clinical cases. In addition, mutations in *MADH4* (encoding SMAD4), which cause a juvenile polyposis/HHT overlap syndrome, have been described, and recently, an HHT3 locus on chromosome 5 (5q31.3–5q32) has been reported. The mutated genes in HHT encode proteins that modulate transforming growth factor-β superfamily signaling in vascular endothelial cells. Management of patients has changed considerably in the last 20 years, in terms of both treatment and the prevention of complications. The goal of this review was to describe the underlying molecular and cellular physiopathology, explore clinical and genetic diagnostic strategies for HHT, and present clinical management recommendations in order to treat symptomatic disease and to screen for vascular malformations.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) (OMIM# 187300) is a predominantly inherited genetic vascular disorder characterized by recurrent epistaxis, cutaneous telangiectasia and visceral arteriovenous malformations (AVMs) that affect many organs, including the lungs, gastrointestinal tract, liver, and brain [1].

In France, the Rendu–Osler rare disease network was created in 2000, and has 13 coordinated clinical teams throughout France and one center in North Italy. In 2004, the Reference Center for HHT was set up in Lyon as part of the French Rare Illness Plan. This center is now working in collaboration with 12 competent centers to optimize patient management. This collaboration between HHT centers and the French National Authority for Health has made possible a national guideline, which may be helpful in improving patient care. The data are easily accessible on the internet at http://www.has-sante.fr/portail/upload/docs/application/pdf/2009-11/ald_31_pnds_rendu_osler__web.pdf.

Epidemiology

Demographic and genetic research on HHT in France began in the 1970s and made it possible to analyze the frequency of the disease at regional and national levels. A large national survey carried out between 1982 and 1986 showed major incidence disparities in France between *départements*, ranging from a maximum of one case per 3375 inhabitants to a minimum of one per 126 000 [2]. Along with a genealogical study, the chromosomal location of one of the two major genes whose mutations cause the disease was first identified on chromosome 12 [3]. More recently, it has been shown that a founder effect associated with the c.1112dupG mutation of the *ACVRL1* gene is responsible for a higher concentration of HHT patients in certain areas than in the rest of the country [4].

Genetics and physiopathology

Three genes are associated with HHT: HHT type 1 results from mutations in *ENG*, coding for endoglin [5] (OMIM#187300), which is a coreceptor from the transforming growth factor (TGF)-β family; and HHT type 2 results from mutations in *ACVRL1*, coding for the activin receptor-like kinase (ALK)1 (OMIM#600376), which is a type I receptor from the TGF-β

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family [6]. Mutations in either one of these two genes account for most but not all clinical cases. In addition, mutations in *MADH4* (encoding the transcription factor Smad4), which are responsible for juvenile polyposis/HHT overlap syndrome, have been described [7] (OMIM#175050).

Each of the three genes implicated in HHT encodes a protein involved in TGF-β superfamily signaling, indicating that it is important in the pathogenesis of HHT. The superfamily ligands in the TGF-β family [TGF-βs, bone morphogenetic proteins (BMPs), and growth and differentiation factors] bind to heteromeric complexes of type I and type II transmembrane serine/threonine kinase receptors [8,9]. Upon ligand binding, the type II receptor phosphorylates and activates the type I receptor. The activated type I receptor then propagates the signal by phosphorylating a family of transcription factors, known as Smads (Smad1, Smad2, Smad3, Smad5, and Smad8). These receptor-associated Smads bind to Smad4 and translocate to the nucleus, where they modulate transcription in association with other transcription factors. TGF-β signaling can also occur through Smad-independent pathways [10]. The type I receptor, ALK1, propagates its signals via the phosphorylation of Smad1, Smad5, and Smad8 [11]. A model has been proposed in which TGF-βs bind to a TGF-βRII–ALK5–ALK1 heterocomplex on endothelial cells [12]; however, this model is currently under debate. More recently, BMP9 and BMP10 have been found to bind ALK1 with very high affinity, together with the type II receptors, BMPRII, ActRII, or ActRIIB (Fig. 1) [13,14]. The coreceptor endoglin has been shown to increase this BMP9–ALK1 response. ALK1 and endoglin are predominantly expressed on endothelial cells, implying that endothelial dysfunction is the starting point in the pathogenesis of HHT.

The involvement of ALK1 and endoglin in the development of HHT has been further confirmed using various mouse and zebrafish models [15–19]. Target disruption of *Acvrl*1 or *ENG* led to embryonic lethality around embryonic day (E)11.5, although *Acvrl1* inactivation resulted in there being more severe vascular defects visible at E9.5 [20]. The heterozygous *Acvrl*1$^{+/-}$/*Eng*$^{+/-}$ mice developed HHT-like vascular lesions with unpredictable age of onset, severity, and location, similar to what is seen in human cases of HHT. Major histopathologic features of the lesions included thin-walled dilated vessels, hemorrhage, and fibrosis. *Acvrl*1$^{+/-}$ mice had profound liver involvement, and displayed a secondary cardiac phenotype, similar to that observed in human HHT2 patients [21]. *Eng*$^{+/-}$ mice developed abnormalities in the vascular walls, postcapillary venules were dilated, and up to 70% of the vascular wall had no smooth muscle cells [22]. It was recently shown that conditional *Acvrl*1 deletion in endothelial cells led to the hallmarks of HHT vascular phenotypes in a consistent and predictable manner, whereas conditional *Tgfβr2* or *Alk5* deletion did not affect vessel morphogenesis [23]. These data further suggested that HHT might not be a TGF-β disease.

Although the genes that cause HHT have been known for over a decade, the mechanisms that underlie the pathogenesis of HHT remain obscure. There is considerable variability in the manifestations of HHT. A genotype–phenotype correlation can be observed between HHT1 and HHT2 patients [24–27]. In HHT1 patients, epistaxis occurs at a younger age, and pulmonary AVMs (PAVMs) appear at an earlier age and have a higher frequency. In contrast, only HHT2 patients have symptomatic hepatic involvement [27]. The severity, age of onset and locations of the vascular lesions are extremely variable from one individual to another. It has been hypoth-

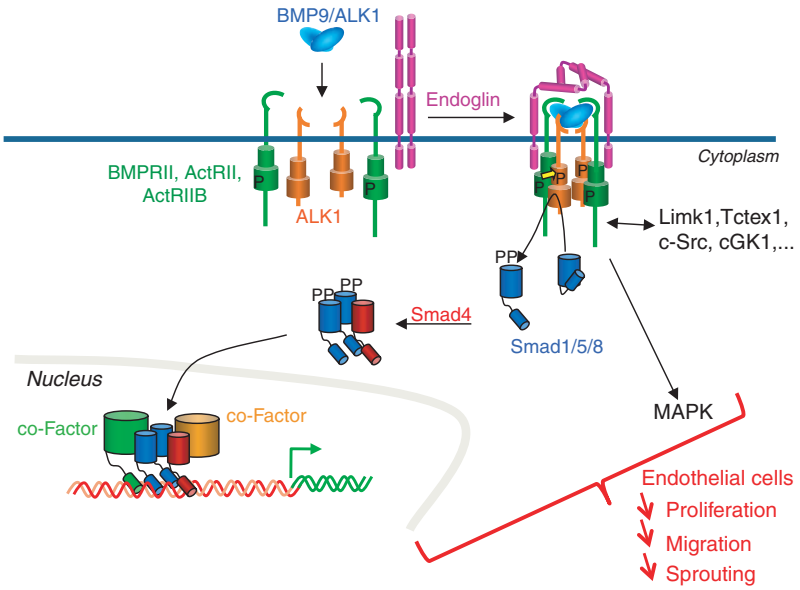

Fig. 1. The bone morphogenetic protein (BMP)9/10 signaling pathways and their functions in endothelial cells. BMP9/10 binding to activin receptor-like kinase (ALK)1 and the type II receptors (BMPRII, ActRII, and ActRIIB) induces Smad1/5/8 phosphorylation and Smad-independent [LimK1, Tctex1, c-src, cGK1, and mitogen-activated protein kinase (MAPK)] signaling pathways, which inhibit endothelial cell proliferation, migration, and sprouting.

esized that the occurrence of AVMs may be influenced by additional factors, such as modifier genes or environmental factors [28,29]. Interestingly, it was shown last year, using mice with an $Alk1^{2loxP}$ allele and endothelium-specific and tamoxifen-inducible Cre driver, that wounding is a second hit that is essential for *de novo* AVM formation in ALK1-deficient subdermal vasculatures in adult stages [30]. This could explain why, in HTT patients, telangiectasia occurs most frequently in the nasal cavity and in areas of the mouth, which are in constant contact with the external environment and subject to chronic inflammation, infections or injuries that induce a reaction similar to the wound response. The brain and lung are two major organs where congenital forms of AVM are often found in HHT patients, and this might be due to persistent angiogenesis after birth in these organs.

The detailed molecular mechanism by which ALK1 and endoglin deficiencies lead to AVM formation remains to be identified. Recently, it was shown that addition of the specific ALK1 ligands, BMP9 or BMP10, inhibited endothelial cell migration, growth, sprouting, and *in vivo* neo-angiogenesis, and may therefore play a role in the maturation phase of angiogenesis (Fig. 1) [13,14,31]. It was also shown that ALK1 signaling inhibited TGF-β-induced vascular endothelial growth factor (VEGF) expression in endothelial cells [32]. It was further demonstrated that BMP9, but not BMP10, was present in blood at an active biological concentration, suggesting that BMP9 could be a circulating vascular quiescent factor [31]. It has thus been hypothesized that HHT could be related to an imbalanced state between antiangiogenic factors (such as BMP9) and proangiogenic factors (VEGF). Taken together, these data suggest that therapies directed against blood vessel formation may be beneficial in HHT.

Diagnosis (Fig. 2)

In order to improve the diagnosis and management of individuals with HHT and to better understand the disorder, the Curaçao criteria for HHT diagnosis were defined in 1999 [1]. A definite diagnosis is made if at least three criteria are present: (i) spontaneous recurrent epistaxis; (ii) multiple telangiectases at characteristic sites (lips, oral cavity, fingers, and nose); (iii) family history (a first-degree relative with HHT); and (iv) visceral lesions (gastrointestinal telangiectasia with or without bleeding, or pulmonary, hepatic, cerebral or spinal AVMs). The diagnosis is definite if at least three criteria are present, possible or suspected if two criteria are present, and unlikely if fewer than two criteria are present.

Molecular diagnosis is available for the *ACVRL1*, *endoglin* and *SMAD4* genes, and mutations are found in about 90% of patients with a definite clinical diagnosis [33]. Molecular diagnosis is currently used in order to screen asymptomatic patients and to avoid complications.

Telangiectases are diagnostic for HHT, and are characteristic if they are found at sites such as the lips, oral cavity,

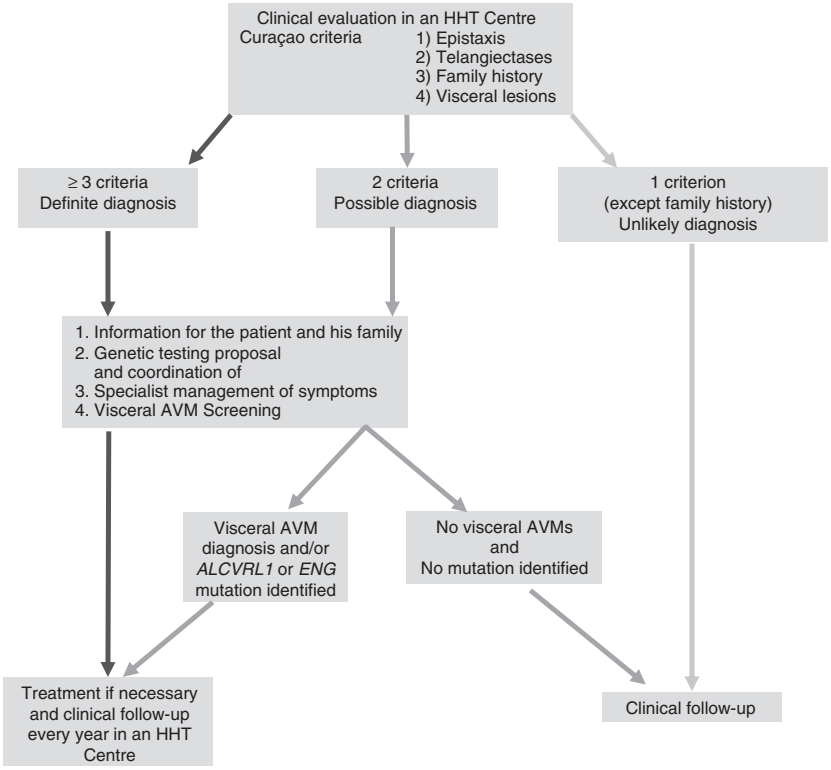

Fig. 2. Hereditary hemorrhagic telangiectasia (HHT) diagnosis and management: decision tree. AVM, arteriovenous malformation.

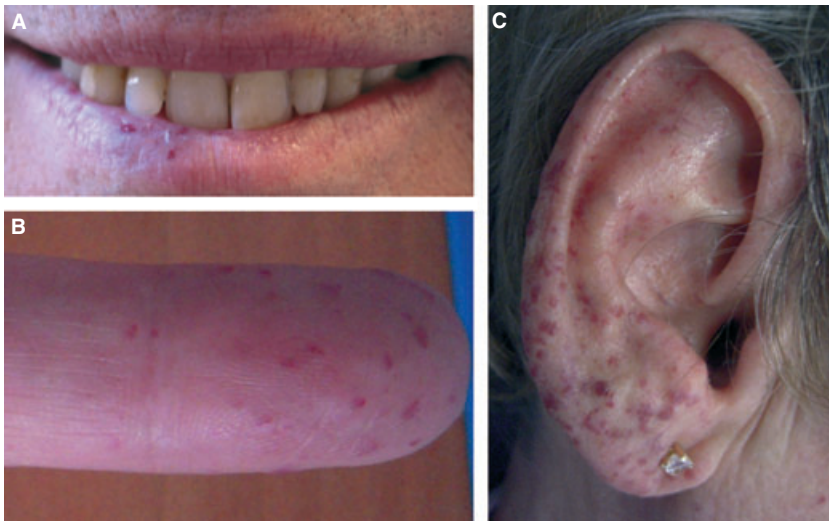

Fig. 3. Mucocutaneous telangiectases of (A) lips, (B) fingers, and (C) ears.

fingers, and nose (Fig. 3). On the face, telangiectases predominantly involve sun-exposed areas [34]. Telangiectases usually develop abruptly, and tend to become more numerous over time.

Epistaxis is the major expression of mucous telangiectases, as a result of its frequency and the handicap that it entails, and 68–100% of HHT patients exhibit telangiectases on the mucous membranes of the nose [35]. Epistaxis affects more than 95% of patients. It is spontaneous, repeated, irregular, diurnal, and nocturnal; it can provoke anemia, and is sometimes incapacitating and socially disruptive. The monthly occurrence of epistaxis is quite variable, with a strong link between variance and the average amount of bleeding. Its objective evaluation is carried out by means of a grid listing the number of nosebleeds per month (variations observed between one and 180) and the duration of bleeding (variations observed between 5 and 840 min). This grid is systematically given by ear, nose and throat (ENT) specialists and network team leaders with instructions for filling in the grid. Now that grid counts are available, the therapeutic gain can be quantified and objectified.

PAVMs (Fig. 4)

PAVMs consist of abnormal communications between pulmonary arteries and pulmonary veins. PAVMs involving several segmental arteries or veins are referred to as complex PAVMs. The incidence of PAVM has been estimated at between 15% and 45% of patients with HHT in previous studies [26,27,36–39], but the exact incidence of pulmonary arterial hypertension in the HHT patient population is not known. In our series, 39% of patients with the *ACVRL1* or *ENG* mutation had PAVM. The incidence of PAVMs appears to be higher in patients with the endoglin mutation, ranging from 49% to 75%, as compared with 5–44% in patients with the activin receptor-like kinase *ACVRL1* mutation [27,40].

PAVMs frequently remain undiagnosed and asymptomatic. They may, however, cause hypoxemia and dyspnea because of right-to-left shunting. PAVMs may also result in severe complications, such as massive hemoptysis or hemothorax, and central nervous system (CNS) complications (transient ischemic attack, stroke, or cerebral abscess). Infections may be related to the right-to-left shunting, which facilitates the passage of septic or aseptic emboli into the cerebral circulation [41].

Severe complications may be the presenting manifestations leading to diagnosis of the PAVM, and justify PAVM screening. Furthermore, treatment of PAVMs significantly decreases the risk of cerebral complications by reducing right-to-left shunting [42,43].

Two tests are currently available for PAVM diagnosis or screening: computed tomography (CT) scans and contrast echocardiography. New-generation CT scans can be carried out efficiently and quickly; a single thoracic CT scan without contrast has the benefit of identifying additional pathologies. Transthoracic contrast echocardiography (TTCE) is a very sensitive test, and consists of injecting microbubbles, which should be removed by the normal pulmonary capillary bed. Right-to-left shunting through pulmonary AVMs results in the appearance of microbubbles on the left side of the circulation. [44]. TTCE has been recommended as the screening test of choice for PAVMs, but a TTCE grading system has not been validated, and this test is operator-dependent. Increased shunt grade predicts increased probability of PAVMs, but is not enough to predict the absence of PAVMs. However, false-negative test results constitute a limit to the use of TTCE, and do not rule out the use of chest scans. The choice of TTCE is now linked to each team's work habits and to the sonographer's experience. A multidetector-row helical CT scan of the chest is

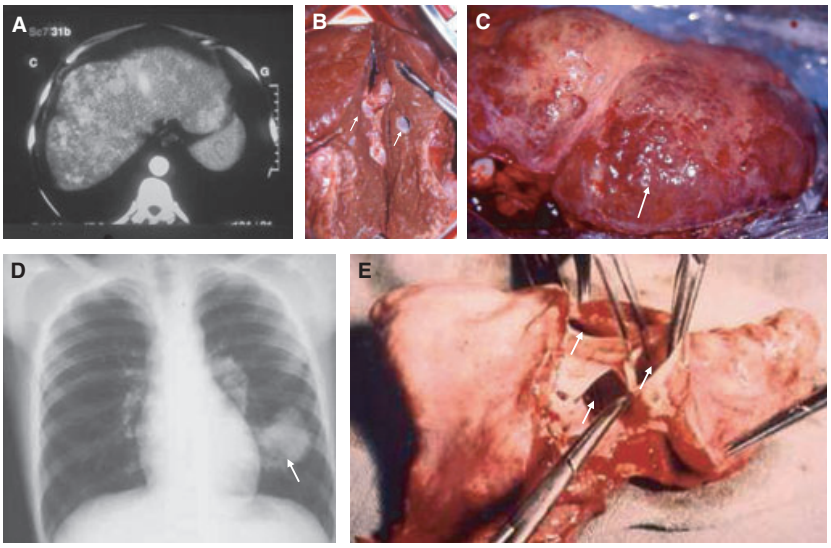

Fig. 4. Arteriovenous malformations (AVMs) observed in hereditary hemorrhagic telangiectasia. (A) Hepatic AVMs on computed tomography scan. (B, C) Macroscopic examination showing larger and dilated vessels. (D, E) Pulmonary AVMs on (D) chest X-ray and (E) after surgery.

now the reference standard for diagnosing PAVMs, based on the presence of a nodular or rounded opacity of variable size, with both afferent and efferent vessels. The sensitivity of chest CT has been shown to be 97% [45].

Hepatic AVMs (HAVMs) (Fig. 4)

Hepatic involvement, defined by a spectrum of arteriovenous malformations, is observed in up to 74% of patients [46], but no more than 8% of those patients will have symptomatic liver disease [47]. Three different types of intrahepatic shunting can be observed: hepatic artery to hepatic veins, hepatic artery to portal veins, and portal veins to hepatic veins. These shunts may lead to high-output cardiac failure (HOCF), biliary ischemia, portal hypertension [48], encephalopathy, or mesenteric ischemia. High cardiac output is the most frequent complication of HAVM, and must be considered carefully. Its development is very slow and is often underestimated by patients. The first signs include slowly worsening dyspnea on effort, combined with asthenia, and then heart rate disorders, such as atrial fibrillation related to atrial dilatation, and signs of first right, and then left, heart failure [49].

The reference standard for diagnosing hepatic involvement in HHT is selective angiography of the hepatic artery. However, this is an invasive, labor-intensive and expensive procedure. Therefore, Doppler ultrasound [50,51] and CT scan are proposed as non-invasive approaches for the diagnosis and monitoring of hepatic HHT lesions [46]. According to the International consensus [47], Doppler ultrasound is sufficiently accurate and suitable for first-line imaging of the liver in the general HHT population. Doppler ultrasound in HHT is used to study hepatic artery diameter and changes in the hepatic artery and its branches, peak flow velocity and resistance index, portal vein velocity, and hepatic vein diameter abnormalities. Direct visualization of shunts (arterioportal, arteriosystemic, and portosystemic) is not possible, as in CT scans. New tools using specialized, contrast-specific ultrasound are currently being studied. Furthermore, echocardiographic monitoring is an important element, as it examines increased cardiac output by measuring the cardiac index.

Cerebral and spinal AVMs

In HHT, CNS involvement is present in up to 10–23% of HHT patients [52,53]. No specificities have been observed in HHT, and all types of congenital vascular malformation (CVM) can be found. However, arteriovenous fistulae (AVFs) occur in young children under 5 years, whereas micro-AVMs and small AVMs typically occur later in life [54]. A different pattern has been observed for spinal AVMs in HHT, which are usually AVFs and affect the pediatric population [55]. A wide range of symptoms can lead to the discovery of cerebral or spinal AVMs. These include headaches, acute or subacute hemorrhage, and back pain in spinal AVMs, with paraparesis or tetraparesis, which can be acute or progressive. There may be sciatic pain, and sphincter disturbance. The bleeding risk of CVMs in HHT has been estimated retrospectively at 0.5% per year [56], but no prospective study is available. Catheter angiography remains the reference standard for diagnosis of cerebral or spinal AVMs.

Gastrointestinal AVMs

Telangiectases can be found anywhere in the gastrointestinal tract, but the stomach and upper duodenum are mainly affected. A prospective study using esophagogastroduodenoscopy to screen small-bowel telangiectases showed that 56% of HHT patients had telangiectases, and more than

70% of patients have gastric or small intestinal telangiectasia [27,57–59]. However, only patients with gastrointestinal hemorrhage or severe anemia unexplained by the epistaxis are explored by endoscopic screening, and the exact incidence is not known. Gastrointestinal bleeding, which affects 15–45% of HHT patients [60,61], may lead to blood transfusion dependence, can be difficult to manage, and may be lethal [62].

Endoscopic evaluation is considered to be the reference standard test for evaluation of gastrointestinal bleeding in HHT patients and, if negative, can be complemented by small-bowel videocapsule endoscopy, which allows for safe and non-invasive exploration of the entire small bowel [63].

Management

Epistaxis

Treatment for acute epistaxis can include compressing techniques, use of wicks made of spongy and resorbable material or expansive, resorbable gels, and selective, bilateral embolization or surgical ligature of the vessels. Long-term management of epistaxis still needs to be optimized [64]. Depending on the severity and disability caused, different ENT techniques may be used: laser [65] and sclerosing drugs, vascular embolism of red spots on the nose and septal dermoplasty [66]. The incomplete efficacy of these therapies has inspired a new search for adjuvant medical treatments that would greatly diminish daily iron loss.

Treatment with estrogens and progestogens [67] has been tested with some success, but the treatment is somewhat problematic in men, and the indication for these drugs in menopausal women aged over 50 years is debatable, with recent observations showing their adverse carcinogenic and cardiovascular effects.

Tranexamic acid, an antifibrinolytic drug, has been used in the treatment of HHT-related epistaxis [68–70] and is widely prescribed in European countries, but has never been evaluated in a totally persuasive manner. A European study is currently being conducted in order to test the efficacy of tranexamic acid in the treatment of HHT. Finally, a few case reports have reported the apparent efficacy of antiangiogenics, which have not yet been studied formally [71].

Management of anemia is still a key element, and iron replacement therapy is advised for any patient with repeated epistaxis leading to long-term iron deficiency anemia. Patients who are intolerant of oral iron can be treated with an intravenous preparation.

Telangiectasia

The use of a long-pulsed Nd:YAG laser is efficient and safe for the treatment of cutaneous and labial telangiectases in patients with HHT [72–74]. The use of skin grafts in the management of painful bleeding ulcers of the fingertips secondary to HHT can be a useful therapeutic option.

PAVMs

All patients with PAVMs must be informed of the risk of infection, and receive a prophylactic antibiotic regimen that is the same as that offered to patients with moderate risk valvulopathy [75]. There is a paradoxical embolism risk, which is a contraindication for all deep-sea diving activities.

Transcatheter vaso-occlusion of PAVMs with detachable steel coils has become the mainstay of treatment. It has been found to be efficacious and to have a good safety profile [42,76–82]. Less frequently, detachable balloons or Amplatzer occluders can be used to treat PAVMs with a very large feeding artery. Treatment of PAVMs is particularly indicated when the feeding vessel of the PAVM is ≥ 3 mm in diameter [76]. Pulmonary artery pressure (PAP) is measured during the examination, which, in adults, is carried out under general anesthesia. Prophylactic antibiotics may be given intravenously during the procedure.

HAVMs

Most patients with hepatic involvement in HHT are asymptomatic and do not need to be treated. The intensive treatment approach is recommended for symptomatic liver shunts, and depends on the type of complication. HOCF is first treated medically using diuretics and β-blockers, plus correction of the anemia and arrhythmia (atrial fibrillation). Portal hypertension should be treated as is recommended for cirrhotic patients. Biliary necrosis has a poor prognosis and is treated with antibiotics. Orthotopic liver transplantation (OLT) should be considered only in patients failing to respond to intensive treatment. Embolization of arteriovenous liver fistulas leads to complications such as hepatic or biliary necrosis [83], and is currently not recommended. OLT has been proposed as the only definitive curative option for HAVMs in HHT in cases of biliary necrosis and cardiac failure [84–86]. However, the optimal timing for liver transplantation is still under discussion, as the mortality and morbidity rates following transplantation remain a limiting factor. Finally, two case reports have recently presented the use of an antiangiogenic treatment (the anti-VEGF antibody, bevacizumab), with spectacular improvements in patients with HHT complicated by severe liver involvement and cardiac impairment [87,88]. A phase II study on the efficacy of bevacizumab in severe hepatic forms of HHT associated with HOCF is ongoing (ClinicalTrials.gov Identifier #NCT00843440).

Cerebral and spinal AVMs

Clearly, complicated cerebral or spinal AVMs must be treated. According to the literature, the rate of major repeat bleeding in unoperated symptomatic patients with AVMs is 4.0% per year, and the mortality rate is 1.0% per year [89]. Various therapies for spinal and cerebral AVMs have been proposed, including surgical resection, stereotactic radiosurgery, embolization, and a combination of these treatments.

Regardless of the method chosen, the treatment of cerebral AVMs must be carried out in a center that has experience with neurovascular diseases. Treatment of asymptomatic cerebral AVMs is more controversial.

Gastrointestinal AVMs

Medical treatments have not shown any benefits. Treatment of iron deficiency and anemia includes iron replacement and blood transfusions if necessary. Currently, local endoscopic therapy, using argon plasma coagulation or an Nd:YAG laser, is recommended to prevent relapse of gastrointestinal bleeding [90–92].

Screening for AVMs

In adults

Nasal vascular abnormalities A blood count and serum ferritin determination will detect anemia and iron deficiency.

PAVMs Screening for PAVMs must include a 'low-dose' volumetric spiral chest CT scan without injection, with a fine section studied with maximum intensity projection (MIP). If the CT scan is negative, a contrast echocardiograph should be considered; if positive, this will justify prophylactic antibiotics. This may be proposed as the first-line screening test unless a prior chest X-ray has already detected an obvious PAVM.

HAVMs According to the Lyon consensus conference [47] and in the current state of knowledge, first-line screening includes ultrasound and liver Doppler ultrasound with measurement of the diameter of the vessels and flow velocity or other aspects particular to HHT. Initial monitoring in cases of clinical liver involvement associated with HHT includes an echocardiogram (with, in particular, evaluation of cardiac flow rate or cardiac index and PAP). Precise identification of particular radiologic liver manifestations and focal liver lesions, in relation to HHT, may require the use of a CT scan or nuclear magnetic resonance imaging.

Cerebral and spinal vascular abnormalities In the absence of a benefit/risk ratio evaluated by means of systematic screening, adult patients can be offered non-invasive brain or spine imaging [magnetic resonance imaging (MRI) or angioscanner] to screen for cerebral or medullary AVMs.

Gastrointestinal vascular abnormalities There is no advantage to systematic screening for gastric angiomas that are asymptomatic, as the preventive actions have not yet shown themselves to be of any benefit. Investigation is only justifiable when there are warning signs: hematemesis or melena, or anemia that is either inexplicable or that worsens very suddenly. Investigations should include a gastroscopy and a coloscopy. If the results are negative, videocapsule examination can be considered.

In pediatric cases

PAVMs As the first step, it may be useful to screen for large PAVMs by means of frontal and profile lung X-rays. If no PAVMs are visible on the chest radiograph, screening for PAVMs can include contrast echocardiography, performed by a sonographer experienced in pediatric cardiology, if the child is cooperative and ≥ 5 years of age. If the contrast echocardiography does not show any shunt, CT scanning is not recommended, owing to the radiation exposure, except in cases with highly suggestive symptoms. If the echocardiography does suggest that there is a pulmonary shunt, a fine section volumetric 'low-dose' helical chest scan examination with MIP is recommended.

HAVMs There is currently no justification in either children or adolescents for proposing screening with ultrasound and liver Doppler ultrasound.

Cerebral and spinal vascular abnormalities To the extent that early, serious neurologic complications have been described, in children in whom the diagnosis of HHT is certain or who are carriers of the genetic mutation, brain and spine MRI with injection of a contrast product as a means of screening for cerebral and/or spinal AVMs without general anesthetic can be considered, either before the age of 6 months or after the age of 6 years.

Gastrointestinal vascular abnormalities There is no advantage to systematic screening for gastrointestinal angiomas that are asymptomatic, as the preventive actions have not yet been shown to be of any benefit.
Gastrointestinal investigations are only justifiable when there are warning signs: hematemesis or melena, or anemia that is either inexplicable or that worsens very suddenly.

Pregnancy It is strongly recommended that screening for PAVMs and neurologic AVMs be carried in women prior to their first pregnancy [93].
During pregnancy, if the patient has any manifestations that are likely to have a negative impact on the prognosis of either the fetus or the mother, a chest scan may be indicated. Symptomatic PAVMs that are detected may be treated by vaso-occlusion during the pregnancy by experienced, multidisciplinary teams [94–99].

Conclusions

Wider understanding of HHT is essential for improving the management and screening of visceral complications. The work of worldwide HHT patient associations and scientific meetings on HHT are helping to achieve this. Antiangiogenic treatments are extremely promising for patient management, although further studies are needed if there is to be conclusive evidence of the efficacy of these treatments.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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