Hereditary hemorrhagic telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant multisystemic vascular dysplasia with a wide ethnic and geographic distribution and a prevalence of more than 1/10,000.[1-4] It is characterized by telangiectases and arteriovenous malformations (AVM), direct artery-to-vein connections predisposing to shunting and hemorrhage (Figure 1). Although the number and location of the lesions vary widely, even within the same family, most of the telangiectases are found in the oral, nasal, and gastrointestinal mucosa and the fingertips, whereas AVM occur mostly in the lungs, liver and the central nervous system.

HHT is a genetically heterogeneous disorder presently linked to two loci: HHT1 (OMIM: 187300) and HHT2 (OMIM: 600376). HHT1 is caused by mutations of the endoglin (*ENG*) gene, localized to the long arm of chromosome 9 (9q33-q34.1),[5,6] while HHT2 is caused by mutations of the activin receptor-like kinase 1 (*ALK1*) gene, localized on the long arm of chromosome 12 (12q11-q14).[7] Both *ENG* and *ALK1* encode transforming growth factor-β (TGFβ) receptor proteins expressed on endothelial cells.[8,9] Endoglin is an accessory TGFβ receptor (TβR),[10] whereas ALK1 is a type I TβR (TβR-I).[11] TGFβ signaling occurs through phosphorylation of TβR and Smad, and the signal is transmitted to the nucleus via pSmad4, which then regulates transcription of the target gene(s).[12,13] Both endoglin and *ALK1* act as positive regulators of angiogenesis, which is a two-phase event: activation and resolution. In the activation phase, mesenchymal cells differentiate into smooth muscle cells and pericytes. New vessels are formed via endothelial cell proliferation and migration. *ALK1* induces endothelial cell proliferation and migration, part of the activation phase, whereas ALK5 (TβR-I) induces the resolution phase. Proper angiogenesis requires an ALK1/ALK5 balance and endoglin appears necessary to maintain this balance.[14,15] Hence, by mechanisms not currently well elucidated, mutations in the ENG and ALK1 cause errors in angiogenesis that give rise to telangiectases and AVM.

Animal studies have provided more insights on HHT pathogenesis. Studies with *Eng*$^{-/-}$ and *Alk1*$^{-/-}$ mice showed that the early steps of vessel formation appear normal, supporting the hypothesis that these genes have a role in angiogenesis rather than vasculogenesis.[16] We also learned from these studies that endothelial expression of endoglin and Alk1 is required for development of vascular smooth muscle cells as well as for communication between the endothelium and the mesenchyme.[17] Additionally, through regulation of Efnb2, a molecular marker of the arteries, Alk1 plays a role in arterial identification.[18] Although the clinical importance of Efnb2 regulation by Alk1 remains undetermined, it may account for some of the clinical differences between *HHT1* and HHT2. One of the puzzling aspects of HHT is the size, number and location of telangiectases and AVM, and the onset of related symptoms is extremely variable between individuals even in the same family with the same inherited mutation. Histopathologic examination of *Eng*$^{+/-}$ and *Alk1*$^{+/-}$ mice showed similar findings in most tissues, yet the disease manifestation, the severity and the localization of the symptoms varied, closely resembling the clinical spectrum of HHT.[19,20] Moreover, *Eng*$^{+/-}$ mice with a 129/Ola background are more susceptible to disease, suggesting the importance of modifier genes in disease pathogenesis.[19] The recent finding of *SMAD4* mutations in patients with a syndrome of juvenile polyposis combined with HHT also implies the role of genetic modifiers, since the same mutations have been found in patients with juvenile polyposis alone.[21]

The existence of HHT families without mutations mapping to either of these genes suggests that at least one more, as yet unidentified, gene may be a rare cause of HHT.[22] In theory, any disturbance of the interaction of the TGFβ pathway proteins with each other, or with other proteins, could cause and/or alter the expression of HHT. In addition to studies showing increased plasma levels of vascular endothelial growth factor (VEGF) in HHT patients,[23] increased VEGF expression was recently demonstrated to cause abnormal microvessels in *Eng*$^{+/-}$ mice.[24] Hence, any condition that stimulates VEGF expression might affect the HHT phenotype. In this issue of the journal, Sadick and colleagues report that VEGF expression is increased not only in the plasma but also in the nasal mucosa of HHT patients (see page 818). As is frequently the case, their finding raises more questions than it answers, such as expression levels in the inactive phase, in asymptomatic mutation carriers, and in patients with non-HHT related epistaxis.

The percentage of *ENG* and *ALK1* mutations thus far reported as causing HHT is similar (53% and 47%).[25] There are no striking mutation hot spots in either gene and more than 90% of the mutations are previously unreported. Although it is not yet certain whether *ALK1* and *ENG* mutations cause HHT by a haplo-insufficiency or a dominant-negative mechanism, haplo-insufficiency, or the reduction of the protein level at the vascular endothelial cells by approximately one half, is suggested by most evidence to date.

Abnormal vessel formation is the basis of the clinical symptoms in HHT. Nosebleeds due to telangiectases in the nasal mucosa are the most common and usually the earliest symptom of HHT. As many as 95% of affected individuals eventually experience recurrent epistaxis, with a mean age of onset at about 12 years and mean frequency of 18 episodes per month. Although severe nosebleeds cause chronic anemia in some patients, others have mild, infrequent nosebleeds that require no treatment. There is a general tendency for nosebleed frequency and severity to increase with age, but some patients report no particular change in their nosebleeds over time and some even an improvement.[26-28] Multiple telangiectases of the hands, face and oral cavity (Figure 2) occur in a similar percentage of patients but the age of onset is generally later than for epistaxis.[27-28] It is common for patients to report first noticing telangiectases in one or more of these locations in the decade between 30 and 40 years old. Telangiectases in these locations are less commonly the source of troublesome bleeding. Telangiectases can occur anywhere in the gastrointestinal tract of HHT patients, but most commonly in the stomach and upper duodenum. About 25% of individuals over the age of 60 will have gastrointestinal bleeding, usually present-

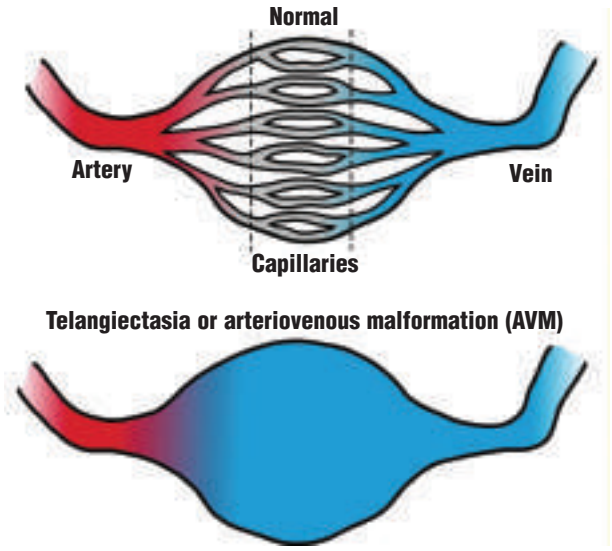

Figure 1. Drawing of a normal blood vessel (top) and a telangiectasia/arteriovenous malformation (bottom).

ing with melena or anemia. Bleeding tends to be slow but persistent and may increase in severity with age.[29] In contrast to the smaller telangiectases, the symptoms of the larger, internal AVM are often not secondary to hemorrhage. Complications of AVM most often occur as a result of shunting of blood, thrombosis or embolus. Pulmonary AVM occur in approximately 30% of individuals with HHT (Figure 3).[30,31] They are thought to be congenital but may enlarge over time.[32] They may be asymptomatic for many years and present insidiously or dramatically with respiratory symptoms such as exercise intolerance, cyanosis or pulmonary hemorrhage, migraine headaches, polycythemia and clubbing.[33-36] However, about 30-40% of individuals with pulmonary AVM will have a central nervous system presentation with thrombotic and embolic events such as stroke, brain abscess or transient ischemic attacks, due to shunting from the right-to-left circulation. This can occur even in the presence of near normal pulmonary arterial oxygen tension.[37] It is common for several adverse events to occur before a pulmonary AVM is identified as the source of the central nervous system (CNS) events.[38] Pregnant women with untreated pulmonary AVM are at high risk of pulmonary hemorrhage.[39]

Central nervous system AVM are also thought to be congenital. Cerebral AVM occur in at least 10% of individuals with HHT[30,40] and may present at any age as seizure, headache, stroke or intracranial hemorrhage.[41,42] They may present neonatally, in infancy or in childhood in otherwise asymptomatic children[43] (Figure 4). Spinal AVM are less common, occurring in about 1% of individuals with HHT. They may manifest as subarachnoid hemorrhage, progressive myelopathy, radicular pain or sphincter disturbance.[44]

Although often clinically silent, hepatic vascular lesions (shunts) can present as high-output heart failure, portal hypertension, biliary disease and portosystemic encephalopathy.[45-48] Hepatic vascular lesions include intrahepatic shunts of different types and disseminated intraparenchymal telangiectases.[46] The prevalence of hepatic involvement in HHT is unknown, but in one study

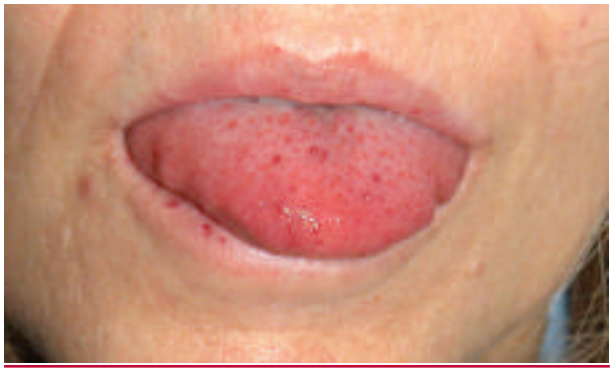

Figure 2. Telangiectases on the lip and tongue of a 53-year old with HHT.

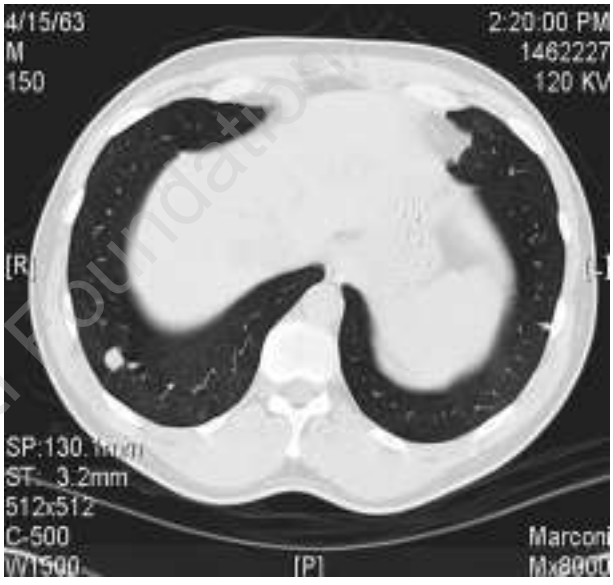

Figure 3. Pulmonary AVM by chest CT.

hepatic vascular abnormalities were identified by computed tomography in 78% of consecutive HHT patients.[47] Most remain asymptomatic. AVM have been described only rarely in other locations including coronary arteries[49,50] and vessels of eye,[51,52] spleen,[53] urinary tract[54] and vagina.[55]

Pulmonary disease indistinguishable from primary pulmonary hypertension has been reported in multiple patients with HHT and mutations in the *ALK1* gene. This suggests that mutations in *ALK1* may lead to occlusion of the pulmonary arteries as well as vascular dilatation manifested as telangiectases and arteriovenous malformations.[56]

Diagnosis

The initial diagnosis of HHT in a family still relies on clinical examination, medical history and family history (Table 1).[57] *De novo* mutations are rare and penetrance approaches 100% by the age of 40. It is thus very uncommon for an individual with HHT to have a negative family history with regards to manifestations of HHT upon

Table 1. Diagnostic criteria for HHT.[57]

HHT is diagnosed in an individual who meets 3 or more of the following diagnostic criteria. The diagnosis is considered possible or suspected when 2 are present and unlikely when fewer than 2 are present:

- Spontaneous, recurrent epistaxis. Nocturnal nosebleeds heighten concern for HHT.
- Mucocutaneous telangiectases, especially on lips, tongue, oral cavity, fingers and nose.
- Internal AVM(s) (pulmonary, cerebral, hepatic, gastrointestinal, spinal). First-degree relative with HHT according to these criteria.

careful questioning. Molecular diagnosis of *HHT* is primarily based on sequencing of the entire coding regions of the *ALK1* and *ENG* genes. The lack of common alleles or mutational types causing this disorder has made the development of simple and sensitive diagnostic tests difficult. The mutation detection rate via sequencing is approximately 70% and novel sequence variants of uncertain clinical significance are common (*unpublished data*). The frequency of big deletions/duplications is unknown and the presence of a third *HHT gene* is still questionable. Thus, a *negative* genetic test for HHT does not rule out HHT. Furthermore, a disease-causing mutation is identified (a *positive* test result) in only slightly more than half of all patients clinically known to have HHT. An individual who meets clinical diagnostic criteria for HHT should be tested first in each family to determine whether the family's HHT mutation can even be detected. Genetic testing for HHT in other relatives is not helpful unless a definitive mutation is detected in this clearly affected index case.

Management

Medical management of patients with HHT is focused on symptomatic treatment for bleeding mucosal telangiectases, and prevention of potentially catastrophic complications of larger, internal AVM, particularly those in the lung and brain. Given the multi-system nature of the disorder, the medical management involves many types of specialists, thus multidisciplinary HHT specialty centers have evolved internationally. Ideally, the multidisciplinary team includes an ear, nose and throat surgeon, interventional radiologist, pulmonologist, neurologist, neuroradiologist, neurosurgeon, geneticist, cardiologist/echocardiographer, gastroenterologist, hepatologist and hematologist. A list of multidisciplinary specialty clinics for HHT can be found on the web site of the HHT Foundation International (*www.hht.org*).

Initial evaluation at the time of diagnosis should include: (i) contrast echocardiography to screen for intrapulmonary shunts[58] and if a shunt is found, computed tomographhy of the chest with 3 mm cuts to characterize the pulmonary AVM;[59] (ii) magnetic resonance imaging of the brain to screen for cerebral AVM;[40] (iii) auscultation for a hepatic bruit and medical history for symptomatic liver shunts.

Pulmonary AVM with a feeder vessel of over 3 mm should be treated to reduce risk of embolic events.[60] Pulmonary AVM are treated using transcatheter embolization, ideally by an interventional radiologist who regularly treats HHT patients and is familiar with the risks associated with these high-flow lesions and their treatment.[37,61] Pulmonary AVM may grow in size over time, so the smaller lesions detected need to be followed.[32] Life-long periodic surveillance for pulmonary AVM is recommended, but the frequency and method depend on the age of the patient and the clinical situation. To prevent cerebral abscess, antiobiotic prophylaxis is recommended for dental and surgical procedures in any patient with evidence of an intrapulmonary shunt.

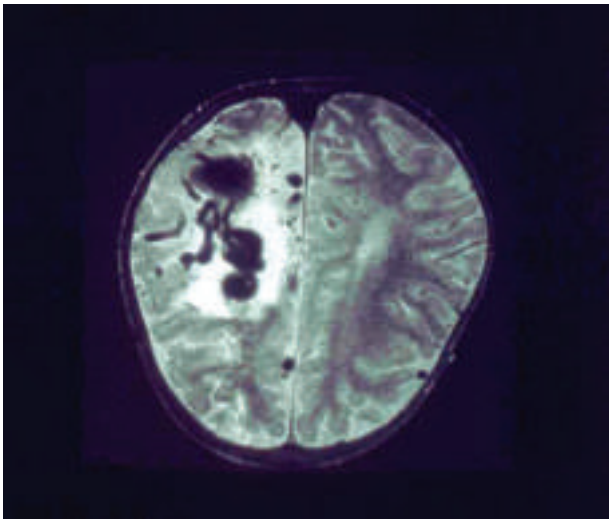

Figure 4. Cerebral AVM by MRI.

Techniques currently used to treat CNS AVM include transcatheter embolization, resection and stereotactic radiosurgery.[62,63] Generally, the long-term risks of hemorrhage, neurological deficits, or death when cerebral AVM are managed conservatively are considered unacceptable.[62,64]

Hepatic AVM on the other hand are not treated in asymptomatic patients. This is due to the fact that they rarely present suddenly or catastrophically and that embolization, so successful in treating pulmonary AVM, results in a high mortality due to liver infarction.[48,65,66] At present, liver transplant is the treatment of choice for patients with otherwise life-threatening symptoms secondary to hepatic shunts.[67] Mild epistaxis is best managed conservatively with humidification and the daily application of nasal lubricants.

Careful laser ablation may be the most effective treatment for the control of moderate nosebleeds.[68,69] Most otolaryngologists experienced with HHT recommend avoiding electric and chemical cautery and transcatheter embolotherapy for routine treatment of recurrent nosebleeds. Otolaryngologists adept at septal dermoplasty using split thickness skin grafts have reported good results in individuals with severe epistaxis.[70]

Skin lesions usually require no treatment, but may be treated by laser ablation if they bleed or for cosmetic reasons. Gastrointestinal bleeding can be treated medically including iron therapy, ethinyl estradiol/norethindrone, danazol and aminocaproic acid or by endoscopic application of a heater probe, bicap, or laser.[71] Anemia due to nosebleeds or gastrointestinal bleeding can be controlled with oral or parenteral iron. In some individuals, blood transfusion may be necessary. Medications that interfere

with normal coagulation, such as aspirin and ibuprofen, should be avoided when possible.

HHT1 or HHT2: does it matter which?

Although it has been reported that pulmonary AVM[72,73] are more frequent in HHT1 and hepatic involvement more common in HHT2,[74–76] *HHT* is clinically very heterogeneous. Significant intra-familial as well as inter-familial variations are observed. It is not possible to diagnose subtypes of HHT, i.e. HHT1 or HHT2, based on the clinical presentation. Most manifestations of HHT have been seen in both types. There are individuals in HHT2 families with early and severe presentation of pulmonary AVM and individuals with HHT1 and liver involvement. Knowing the gene involved cannot accurately predict clinical symptoms.[75,77]

In summary, HHT is a relatively common genetic disorder for which mechanisms of disease are only beginning to be understood. Much has been learned in the past two decades about its wide spectrum of clinical manifestations and effective management, however, the diagnosis is frequently missed by physicians treating a particular symptom or manifestation. Both diagnosis and appropriate management of HHT patients require recognition of its multi-system nature and varied presentation. Although the structural defect of the vasculature is similar regardless of the location in the body of a telangiectasia or AVM, the associated risks, recommended screening and optimal treatments are unique to each organ.

Jamie McDonald,° Pinar Bayrak-Toydemir°#*
**Department of Radiology (HHT Clinic),*
°ARUP Laboratories, #Department of Pathology,
University of Utah, Salt Lake City, USA
E-mail: jamie.mcdonald@hsc.utah.edu

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