

# Hereditary Hemorrhagic Telangiectasia (HHT)



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Hereditary tendency of epistaxis was first described by Babington in 1865 in a case report of “severe and violent” epistaxis in a family spanning five generations (1). This heritable tendency for epistaxis was eponymously named, subsequent to published observations of Rendu (2), Osler (3), and Weber (4), and then finally named hereditary hemorrhagic telangiectasia (now shortened to HHT) by Hanes in 1909 (5).

HHT is now recognized as an autosomal dominant disorder of angiogenesis that results in vascular malformations of the skin, mucus membranes, and viscera. These vascular malformations result in morbidity and mortality through a variety of pathogenic mechanisms. Most commonly, patients experience epistaxis. Epistaxis can range from a nuisance to severe bleeding, the latter resulting in blood loss anemia requiring iron therapy or transfusion. Vascular malformations of the brain and spinal cord can bleed and result in neurological injury. Arteriovenous malformations of the lung bypass the normal filtration function of the pulmonary capillary network and allow thrombi and bacteria to gain access to the arterial circulation, thereby resulting in ischemic or infectious neurological complications. Vascular malformations of the liver can result in biliary disease, portal hypertension, or high output heart failure (6,7).

The disordered angiogenesis of HHT is caused by mutations in one of several distinct genes, all of which are components of the signaling pathway for the transforming growth factor-beta (TGF- $\beta$ ) superfamily (7). The most common genes affected are endoglin (*ENG*) on chromosome 9, activin A receptor type II-like 1 (*ACVRL1*) on chromosome 12, and mothers against decapentaplegic homolog 4 (*SMAD4*) on chromosome 18. *ENG* and *ACVRL1* are membrane-bound receptors of the TGF- $\beta$  family, whereas *SMAD4* codes for a transcription factor that is essential for the functioning of this pathway. There are phenotypic differences in HHT depending upon the affected gene (8). Mutations in *ENG* cause HHT 1, mutations in *ACVRL1* cause HHT2, and mutations in *SMAD4* cause HHT, associated with juvenile polyposis. Approximately 85 to 90 percent of patients with HHT have mutations on one of the above referenced genes. The remaining 10 to 15 percent likely have mutations in genes that have yet to be discovered. Mutations in *GDF2* (coding for bone morphogenic protein 9 (BMP 9) and *RASA1* (coding for RAS p21 protein activator) cause vascular-anomaly syndromes with some phenotypic features of HHT (9,10).

The incidence of HHT is estimated at one in 5,000. However, a large percentage (perhaps 70 to 90 percent) of patients are not diagnosed, and there is often a considerable lag time between symptoms and diagnosis (11,12). HHT is diagnosed based upon the Curacao Criteria (13):

1. Epistaxis: Spontaneous, recurrent nose bleeds
2. Telangiectases: Multiple, at characteristic sites (lips, oral cavity, fingers, nose)

3. Visceral lesions: Gastrointestinal telangiectasia, pulmonary AVM, hepatic AVM, cerebral AVM, spinal AVM
4. Family history: First degree relative with HHT according to these criteria

Patients with three or more criteria are considered to have HHT. Patients with two criteria are suspected to have HHT, and patients with fewer than two criteria are unlikely to have HHT.

Telangiectases (Figure 1) occur in 90 to 95 percent of patients, although they are evident in about half of patients prior to age 30 (14). Most commonly they occur on the face (63 percent of patients), mouth (48 percent of patients), and hands/wrists (37 percent of patients). They are rarely a source of morbidity.

Epistaxis also occurs in 90 to 95 percent of patients. In some patients, it can result in blood loss anemia. About 50 percent of patients will have their first nosebleed by the age of 10, and 80 to 90 percent will have nosebleeds by the age of 20 (14). The average frequency of nosebleeds is 18 episodes per month and the average duration is 7.5 minutes per bleed (14, 15). Epistaxis is conveniently quantified using the Epistaxis Severity Score (16), a tool that is available on the CureHHT website (<http://curehht.org>). Management of epistaxis starts with nasal hygiene. Patients are advised to keep the nasal mucosa moist using nasal saline sprays or topical ointments. Patients with epistaxis refractory to nasal hygiene are referred to an otolaryngologist with expertise in HHT for treatment. Improved and sustained control of epistaxis is obtained by combining laser ablation with injection of bevacizumab (Avastin®) into the base of the telangiectasia (17.). Septal dermoplasty (18), or nasal closure (Young’s procedure) (19, 20), are reserved for epistaxis refractory to endoscopic control.

Gastrointestinal bleeding is another cause of blood loss anemia in patients with HHT. Gastrointestinal bleeding from HHT occurs in about 30 percent of patients and is largely confined to patients over the age of 50 (21).

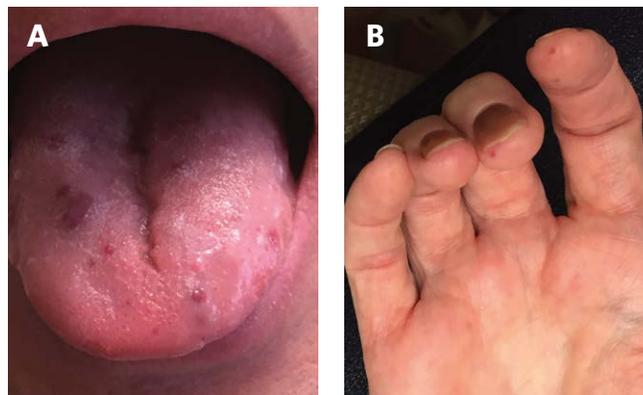
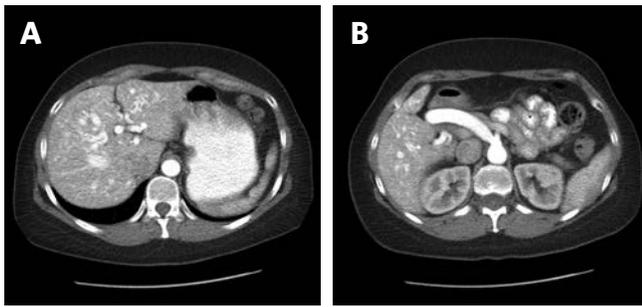


Figure 1. Typical telangiectases of HHT noted on tongue (A) and hands (B).

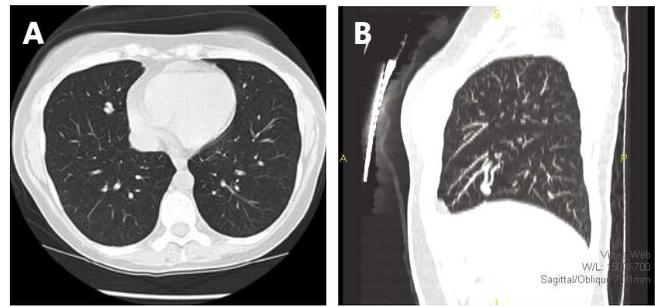


**Figure 2.** Arteriovenous malformations of the liver (A) resulting in hypertrophy of the hepatic artery (B).

Telangiectases most commonly occur in the stomach and duodenum. The presence and extent of telangiectases in the stomach and duodenum predict more distal telangiectases (22). Therefore, gastroduodenoscopy is generally sufficient to diagnose gastrointestinal involvement in HHT. However, video capsule endoscopy has demonstrated frequent involvement of the jejunum and ileum and may be needed in cases where the endoscopic findings do not explain the severity of anemia. Treatment of HHT-related gastrointestinal bleeding is first directed at iron replacement and/or blood transfusion. If the anemia is refractory to iron, patients undergo endoscopic ablation of the telangiectases in the stomach and duodenum. Patients who continue to bleed after endoscopic treatment can be considered for systemic hormonal or antifibrinolytic therapy (13,23).

HHT involvement of the liver (Figure 2) can cause several clinical syndromes. First, HHT can cause high-output heart failure. Due to shunting of cardiac output through hepatic artery-hepatic vein shunts, these patients can have profound exercise limitation. Exercise testing demonstrates low maximal oxygen consumption and early anaerobic threshold. The second hepatic phenotype is portal hypertension, often due to hepatic artery-portal vein shunts. Affected patients will have varices, gastrointestinal bleeding, and ascites. Finally, HHT can cause a cholestatic syndrome which may be due to biliary ischemia (24). Management of hepatic complications of HHT is largely with medical therapy for heart failure and portal hypertension. Embolization of hepatic AVM is not recommended. Liver transplant is performed for patients who are refractory to medical therapy and can yield excellent survival outcomes (25).

Pulmonary complications of HHT include pulmonary hypertension and pulmonary AVM. Pulmonary hypertension occurs in approximately 10 percent of patients with HHT (26). Most patients with pulmonary hypertension have mutations in ACVRL1 (27). Pulmonary arteriovenous malformations (PAVM) (Figure 4) occur in about 20 percent of patients, the predominance of patients having mutation in ENG (8). PAVM can cause hypoxemia (from right to left shunting) and neurovascular complications. Because blood flowing through a PAVM bypasses the normal filtration of the pulmonary capillary network, small venous thrombi and bacteria can gain access to the arterial circulation and can cause strokes and brain abscesses. All patients with HHT are screened with contrast-enhanced echocardiography to detect right-to-left shunt. If shunt is present on echocardiography, a CT scan is performed. PAVM with feeding vessel of 3-mm or larger are referred for embolization. All patients with HHT and right-to-left shunts are advised to receive antibiotic prophylaxis (equivalent



**Figure 3.** Small pulmonary AVM in right middle lobe on the transverse section CT images (A). Note that the feeding artery and draining vein are better seen on the sagittal reconstruction images (B).

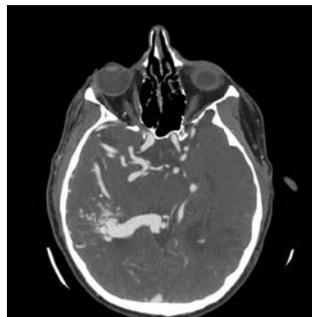
to recommendations for subacute bacterial endocarditis) for dental work. Also, they are advised to have 0.2 micron IV filters employed if possible for any intravenous therapy (to prevent paradoxical air emboli), and finally they are advised against scuba diving (7).

Cerebral arteriovenous malformations (CAVM) (Figure 5) occur in 10 to 20 percent of HHT patients (28, 29). They carry a bleeding risk of 0.4 percent a year, although patients with prior hemorrhage have a bleeding rate of 10 percent a year (30). They occur more frequently in patients with an ENG mutation (i.e. HHT1). Cerebral AVM in patients with HHT are usually multiple and tend to be smaller than in non-HHT related cerebral AVM (31). All patients who are diagnosed with HHT are referred for a brain MRI to screen for CAVM. If present, patients are referred to a neurovascular specialists for consideration of treatment with embolization, radiation therapy, or surgery.

Anemia is a frequent complication of HHT owing to the prevalence of epistaxis and gastrointestinal bleeding. Patients frequently require iron therapy (either oral or intravenous) and in some cases transfusion (13).

In summary, HHT is a rare disorder that frequently goes undiagnosed and can result in stroke, cerebral hemorrhage, or brain abscess. The first step in preventing these complications is timely recognition of the condition followed by screening for, and treatment of, high-risk vascular malformations of the lung and brain. Because the condition is inherited in an autosomal dominant fashion, all first degree relatives of patients with HHT should undergo evaluation and/or genetic testing with prevention of the neurological complications as a goal. Optimally, identification and screening of relatives is done in collaboration with medical geneticist and genetic counselors.

*For a list of references to this article, other articles in this issue, and the Division of PACCM's recent publications and suggested readings for this issue, visit [UPMCPHysicianResources.com/Pulmonology](http://UPMCPHysicianResources.com/Pulmonology).*



**Figure 4.** Right temporoparietal AVM in a patient with HHT. There is a large dilated vein draining the AVM traversing the right lateral ventricle atrium into the vein of Galen.