Distinct Forms of Pulmonary Hypertension Complicate Hereditary Hemorrhagic Telangiectasia

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Pulmonary hypertension (PH) associated with hereditary hemorrhagic telangiectasia (HHT) occurs most commonly as a consequence of high-output heart failure related to excessive shunting through visceral vascular malformations. A smaller number of HHT patients develop a form of heritable pulmonary arterial hypertension, characterized by an elevated pulmonary vascular resistance with normal left heart filling pressures. In this review, we will discuss the clinical manifestations of HHT in general, the pathophysiology behind the different forms of PH associated with HHT, and the clinical care of the HHT patient with PH.

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant vascular disorder that affects up to 1 in 5000 individuals worldwide.[1,2] The disease is characterized by mucocutaneous and visceral vascular malformations, often allowing direct communication between arterioles and venules without intervening capillaries. These malformations appear as small red vascular dilations when they involve small vessels in the skin and mucus membranes and are termed telangiectasia. Larger visceral arteriovenous malformations (AVMs) can be found in the brain, lung, liver, and elsewhere.[3] The clinical diagnosis of HHT is based on the presence of at least 3 of the following criteria: spontaneous recurrent epistaxis, multiple characteristic mucocutaneous telangiectasia, visceral vascular involvement, and a first-degree relative who meets criteria for the diagnosis of HHT (Table 1).[4]

More than 80% of HHT is caused by mutations in 2 genes: endoglin and ACVRL1. Endoglin (ENG, chromosome 9q34.11) is an accessory protein involved in transforming growth factor eta (TGF-β) signaling, pathogenic mutations of which lead to HHT type 1 (HHT1), characterized by relatively early clinical manifestations and an increased likelihood of AVMs in the brain and lungs.[5] ACVRL1 (also known as ALK1, chromosome 12q.13.13) encodes activin-like kinase 1, a type I TGF-β superfamily receptor. Mutations in ACVRL1 lead to HHT type 2 (HHT2), in which liver AVMs are more prevalent, and pulmonary and brain AVMs are seen less frequently.[6] Another 2% of HHT is associated with mutations in Smad4, also known as MADH4, a gene linked to the juvenile polyposis-HHT syndrome.[7] Additional causative genes have yet to be described, but likely participate in the same pathway. Recent work, for example, describes an HHT-like phenotype resulting from mutations in BMP9/GDF2, which functions as a ligand in TGF-β signaling.[8]

The clinical presentation of HHT is variable and depends on the extent and location of vascular malformations. While epistaxis from nasal mucosal telangiectasia is the most consistently observed manifestation affecting over 90%, malformations can arise as vessels develop in virtually any tissue.[3] Pulmonary AVMs are the most common pulmonary vascular manifestation, and are of particular clinical relevance since the resulting right-to-left shunting increases the risk of stroke and brain abscess. Pulmonary hypertension (PH) is an infrequent but important complication of HHT, presenting in 2 distinct forms. Most commonly, PH occurs in HHT as a consequence of high-output heart failure from excessive shunting through visceral vascular malformations, usually in the liver.[9] However, a small number of HHT patients manifest a syndrome of heritable pulmonary arterial hypertension (HPAH), whose clinical features mirror those of idiopathic PAH.[10] PH of either type can have a profound effect on symptoms and outcomes in patients with HHT. For that reason, clinicians that treat patients with PH should be aware of both.

PH FROM HIGH-OUTPUT HEART FAILURE

Most cases of PH in HHT result from high-output heart failure due to shunting through liver AVMs, although systemic shunting outside the liver has also been implicated. Hepatic vascular malformations, once considered infrequent in HHT, are present in over 70% of patients with HHT[11]; however, fewer than 10% will develop symptoms, often when intrahepatic shunting exceeds 20% of cardiac output.[12] Three distinct types of shunt have been described[9]: hepatic artery to hepatic vein, hepatic artery to portal vein, and portal vein to hepatic

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Table 1. Clinical Diagnostic Criteria for HHT

Level of Diagnostic Certainty	Number of Criteria Present
Unlikely	≤1
Possible	2
Definite	≤3

The level of diagnostic certainty of HHT is determined by the presence or absence of 4 clinical features known as the Curacao criteria: recurrent spontaneous nose bleeding, multiple characteristic mucocutaneous telangiectasia, visceral vascular anomalies, and any first-degree relative meeting these criteria.

vein. Any or all 3 types of shunting may be present, but one type of shunt usually predominates, dictating the clinical manifestations when any occur.

High-output heart failure from excessive hepatic artery to hepatic vein shunting—or less commonly from shunting between portal and hepatic veins—is the most common complication of hepatic involvement in HHT. Portal hypertension, biliary necrosis, hepatic encephalopathy, and intestinal ischemia from mesenteric steal can also occur. High-output heart failure typically presents in the seventh decade with nonspecific symptoms such as exertional dyspnea and lower-extremity edema,[9,13] and tends to affect females more than males. Nonetheless, routine screening for liver involvement in HHT is not recommended. In symptomatic patients, various imaging modalities including Doppler ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) may be used to identify hepatic vascular malformations. Lesions are often diffuse and can replace large portions of the liver parenchyma. Detecting more subtle abnormalities such as mesenteric steal or portovenous shunting may require angiography.

Hepatic artery to hepatic vein shunts behave similarly to other extracardiac left-to-right shunts. Increased cardiac preload and decreased systemic vascular resistance are associated with a compensatory increase in cardiac output via increases in both stroke volume and heart rate. As the high output state persists, left ventricular (LV) filling pressures increase, and PH follows.[14,15] Signs of PH and high-output heart failure can be detected on physical examination. Patients may manifest a hyperdynamic precordium, bounding pulses, and a systolic ejection murmur. Hepatic bruit is present on auscultation in most cases, and the liver may be pulsatile. Echocardiography reveals preserved LV systolic function, often with left atrial enlargement. Increases in flow across the LV outflow tract may be misinterpreted as indicative of aortic stenosis rather than high cardiac output. Right ventricular (RV) enlargement and dysfunction are seen in the later stages of the disease and reflect worsening PH. Right heart catheterization demonstrating increased pulmonary artery pressures with high cardiac output and elevated pulmonary artery and capillary wedge pressures confirms the diagnosis in the presence of sufficient intrahepatic shunting. Pulmonary vascular resistance (PVR) is typically normal.

Medical therapy for PH from high-output heart failure, including diuretics, salt restriction, and control of atrial fibrillation (if present) is effective in early stages.[9,13] Anemia from epistaxis or gastrointestinal bleeding should be promptly corrected, since anemia can exacerbate the high output state and further impair oxygen delivery. Pulmonary vasodilator therapy is unlikely to be helpful and may have detrimental hemodynamic effects by increasing pulmonary blood flow.

Definitive treatment of hepatic AVMs has been challenging. Early efforts focused on reducing shunt through surgical ligation or banding of the hepatic artery.[16,17] These measures proved effective at reducing shunting, relieving symptoms of heart failure, and reducing pulmonary artery pressures, but complication rates were high and the benefits were only transient due to revascularization. Transcatheter embolization of hepatic AVMs also effectively reduces shunting and improves symptoms, but the rate of serious complications including death is unacceptably high.[18,19] Up to 30% of treated patients experience complications including severe hepatic and/or biliary necrosis requiring liver transplantation or resulting in death after embolization. For those reasons, the procedure is not routinely recommended and has largely been abandoned in this context except in special circumstances.[20]

The experience with liver transplantation has been more favorable. The first liver transplant for hepatic complications of HHT was performed in 1985, and is now considered the definitive therapy for severe high-output heart failure and secondary PH in HHT. Symptoms resolve in most patients after liver transplantation, with favorable long-term outcomes, including one series that reported 83% 5-year survival following liver transplantation.[21] Still, there has been understandable interest in less morbid but equally effective therapies for high-output heart failure and PH from hepatic AVMs. Encouraging results have been reported with the use of inhibitors of vascular endothelial growth factor (VEGF). In one small, nonrandomized series, administration of bevacizumab was associated with an improvement in echocardiographic measures of cardiac output as well as improvements in dyspnea in HHT patients with high-output heart failure from intrahepatic shunting.[15] In the same series, 5 of 8 patients with PH demonstrated normalization of pulmonary artery pressures by echocardiography. As one might expect, there was no appreciable change in the size of hepatic AVMs, suggesting that the improvements observed may have been due to decreased shunting through the hepatic microvasculature rather than through larger hepatic AVMs.

HPAH IN HHT

Heritable transmission of PAH was initially described in 1954, by Dresdale et al, who reported primary (idiopathic) PAH in 2 sisters and the son of one of the women.[22] Since then, much has been learned about its genetic basis. Mutations in the gene encoding bone morphogenetic protein 2 (BMPR2) account for most cases.[23] Like endoglin and ACVRL1, BMPR2 is a member of the TGF-β superfamily of receptors, part of a highly conserved signaling pathway that controls tissue-specific proliferation, differentiation, and cellular

migration. Mutations in BMPR2 are also prevalent in sporadic cases of idiopathic PAH where they are associated with earlier disease onset and more severe hemodynamics.[24]

Heritable PAH exhibits an autosomal dominant inheritance pattern with unusually low penetrance. A 2-hit hypothesis has been proposed to explain the low penetrance, supported by the finding in 2 families that, in addition to inheriting the pathogenic BMPR2 allele, a mutation in a second TGF-β gene is required to develop PAH.[25] However, nearly 30% of patients with HPAH do not carry mutations in BMPR2. Some of the remaining cases include HHT patients with mutations in ACVRL1, and to a lesser extent, endoglin, that can lead to HPAH[10] that is histologically and clinically identical to that seen with BMPR2 mutations.[26] Most but not all will manifest features of both HHT and PAH, which can present unique challenges in care.

Early symptoms of PAH in HHT are nonspecific and include dyspnea and fatigue that may be incorrectly attributed to other features of HHT like anemia from epistaxis or gastrointestinal hemorrhage, or less commonly from hypoxemia from intrapulmonary shunting. Signs of elevated right heart pressures should trigger an evaluation for PAH in patients with HHT, especially those with ACVRL1 mutations, including right heart catheterization. Hemodynamic measures readily differentiate PAH from PH related to systemic left-to-right shunting. In contrast to PH from high-output heart failure, PAH is characterized by elevated PVR, reduced cardiac output, and preserved left heart pressures.[27]

The pathogenic overlap between HHT and PAH may offer insight into the mechanisms underlying each disease, which requires an understanding of TGF-β superfamily signaling. TGF-β signaling is initiated by ligand binding to a type II TGF-β receptor such as BMPR2, either directly or via an accessory protein, such as endoglin (Figure 1). TGF-β ligands include the archetypal TGF-β as well as bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs), and activin/inhibins. BMP signaling, in particular, is fundamental to cardiovascular and lymphatic development, with mutations in this signaling pathway leading to a range of vascular dysfunction and defects in angiogenesis.[8] Upon ligand binding, type II receptors join with a type I receptor, forming a heteromeric receptor complex. Formation of this complex activates the type I receptor's serine/threonine kinase domain, leading to phosphorylation and activation of receptor-associated cytoplasmic signaling molecules, or receptor Smads (R-Smads). R-Smads complex with Smad4 to translocate to the nucleus and modify gene expression in a cell-specific fashion, in the case of the pulmonary vasculature affecting genes involved in endothelial proliferation, vascular regeneration, and angiogenesis.[28,29]

The precise mechanisms by which alterations in TGF-β signaling lead to PAH or HHT are unknown. Indeed, the vascular dilations of HHT are fundamentally different from the intimal hyperplasia, medial thickening, and plexiform lesions characteristic of PAH. When PAH and HHT coexist, the disparate vascular pathology may result from distinct processes arising from the same genetic defect. In addition, the contrasting pathology may lead to unique pathophysiologic consequences in this population. For example, in HHT patients with PAH and pulmonary AVMs, shunting through pulmonary AVMs could reduce RV afterload and mitigate the effects of PH. If so, it follows that transcatheter embolization of pulmonary AVMs could precipitate RV failure by abruptly increasing RV afterload. Studies in HHT patients with PH primarily associated with high output found no effect of embolization of pulmonary AVMs on pulmonary artery pressures.[30] However, differences in physiology including the lack of pulmonary vasodilator reserve in patients with PAH suggest that this might not be the case in patients with a significantly elevated PVR. Likewise, little is known about the effects of intrahepatic shunting or other left-to-right shunting in HHT patients with PAH. The resulting increase in pulmonary blood flow would be expected to worsen the hemodynamics of PAH, but this circumstance has not been systematically evaluated.

Fortunately, despite involving similar pathways, very few patients with HHT will develop PAH. The exact prevalence of PAH in HHT is unknown, but it is probably less than 1%. One series found no cases of PAH among 111 patients with HHT.[31] Another series using echocardiography reported a higher prevalence of PH, but did not confirm PAH with invasive hemodynamic measures.[32] Whatever its precise prevalence, the vast majority of reported cases of PAH-HHT are seen in patients with ACVRL1 mutations,[10,33] similar to what has been described in cases of PH from high-output heart failure. Endoglin mutations have also been linked to PH, but most cases were observed in the setting of liver AVMs,[27] anorexigen use,[34] or in the absence of HHT.[35] For that reason, controversy exists as to whether HHT-causing endoglin mutations place patients at significantly increased risk of developing PAH.[33]

Nonetheless, a small number of cases of PAH have been reported in patients with endoglin-associated HHT. One case involved an infant diagnosed with idiopathic PAH, only to manifest pulmonary AVMs and characteristic telangiectasia later in childhood.[36] An additional 2 cases were recently reported in a series of HHT patients from China,[37] who met criteria for definite HHT and who had PAH confirmed by pulmonary artery catheterization. Taken together, these case reports and the above studies in HHT suggest that PAH is rare overall and nearly all cases result from mutations in ACVRL1, though a very small number of exceptions may exist.

PAH in HHT is treated similarly to other forms of PAH. There is insufficient experience and no systematic trials to determine the effectiveness of vasodilator therapy or how well it is tolerated in patients with HHT, but case reports involving very small numbers of patients describe improvements in hemodynamics and functional capacity with the use of endothelin receptor antagonist and prostacyclins.[38,39] Higher-quality evidence is lacking because of the rarity of PAH-HHT and because to date few patients with PAH-HHT have been included in trials of vasodilator therapy in PAH.

CONCLUSION

Patients with HHT may come to medical attention because of PH before receiving a diagnosis of HHT; therefore, clinicians who treat PH should have a

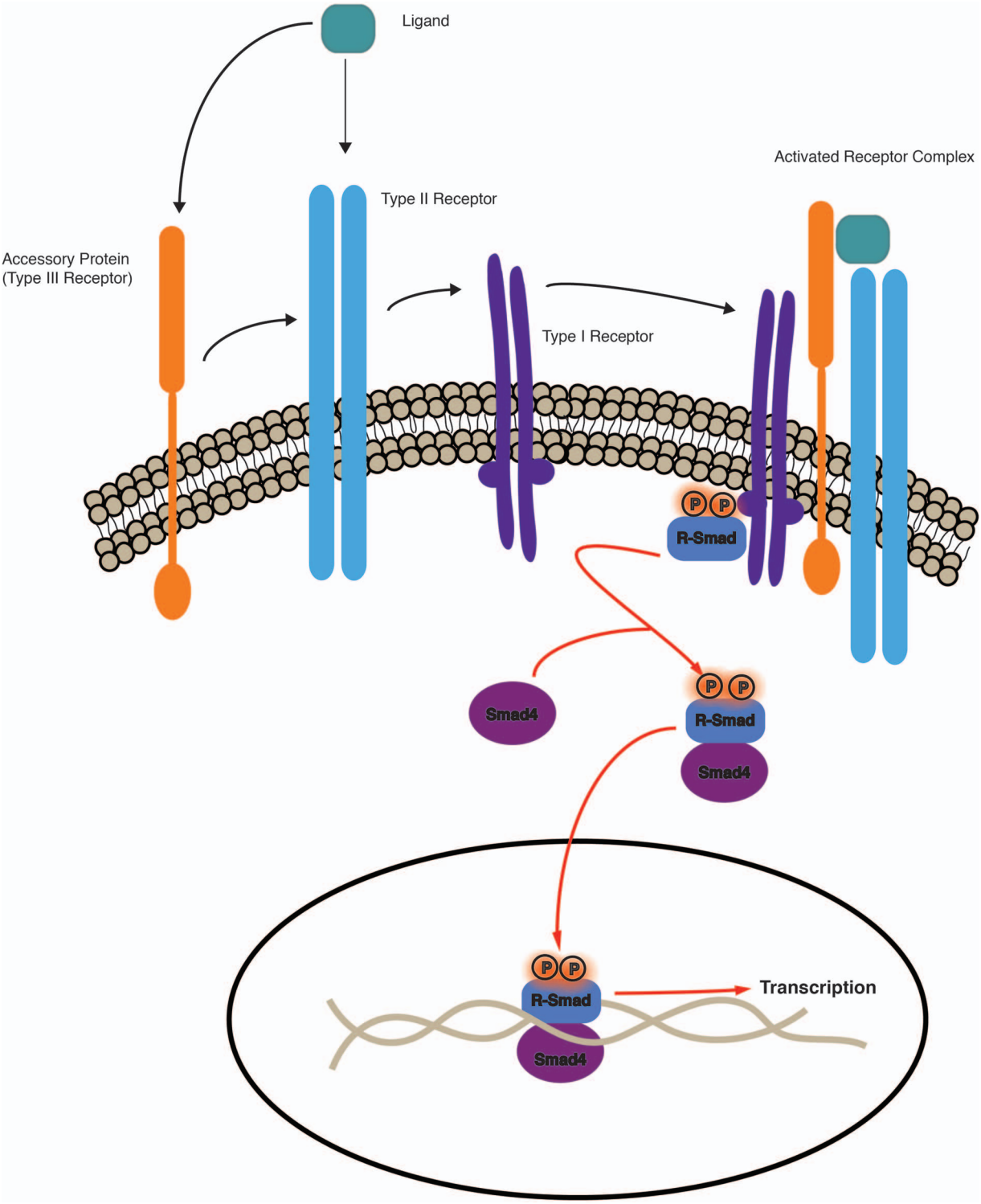

Figure 1: Canonical TGF-βsignaling pathway. TGF-β signaling is initiated by binding of ligands including TGF-βs, BMPs, activin/inhibins, or others to a type II TGF-β receptor. This can occur directly or via an accessory, or type III, TGF-β receptor. The ligand-bound type II receptor can interact with a type I TGF-β receptor, thus forming an activated heteromeric receptor complex, allowing phosphorylation of receptor-associated cytoplasmic signaling molecules (R-Smad 1/5/8). Activated R-Smads associate with Smad4, which chaperones the Smad complex to the nucleus to modify gene expression.

thorough understanding of HHT, its diagnosis, and the ways in which PH can present in HHT. Collaborative care of these patients should include coordination between HHT centers of excellence and centers with expertise in the care of patients with PH. Secondary PH from left-to-right systemic shunting is the more common presentation and responds well to current treatment options with promising new therapies on the horizon. PAH is less commonly seen, but given its seriousness and potential to respond to treatment, any HHT patient with signs of elevated

right heart pressures should undergo thorough evaluation for PAH. Likewise, testing for mutations in the genes responsible for HHT, especially ACVRL1, should be considered in cases of heritable transmission of PAH in the absence of BMPR2 mutations. Ultimately, increased awareness of PH in HHT will lead to more timely diagnosis of these important conditions and may facilitate the development of more effective treatments for both types of PH in HHT.

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