We are delighted to bring you this issue of Respiratory Reader about hereditary hemorrhagic telangiectasia or HHT (Osler, Weber, Rendu syndrome). The HHT Center of Excellence at UPMC and the University of Pittsburgh employs a team of clinical specialists and researchers that is dedicated to providing state-of-the-art care, advancing the understanding of HHT, and contributing to the overall goal of finding a cure. As a result of that collective expertise, this center is designated as one of 18 HHT Centers of Excellence in the United States.

In this issue, Dr. Christopher Faber, medical director of the HHT Center of Excellence, presents a succinct clinical overview of HHT, emphasizing the importance of early recognition and screening in preventing the serious complications of stroke and cerebral hemorrhage.

Dr. Beth Roman, research director, provides insight into the molecular mechanisms of arteriovenous malformation development from her work with a zebrafish model of HHT, specifically underscoring the importance of bone morphogenetic protein 10 (BMP10) in the pathogenesis of arteriovenous malformations.

Dr. Suneeva Madam-Khatarpal, medical director for the Pediatric HHT Center, Dr. Andrew McCormick, medical director of the Vascular Anomaly Center, and Jessica Sebastian, genetic counselor for the HHT Center of Excellence, present a case report illustrating the characteristic inheritance pattern of HHT and highlighting the importance of screening family members of identified patients.

Finally, Kathleen Lindell, PhD, RN, program coordinator, Jessica Romanias, RN, outpatient nurse coordinator, and Melody Porter, patient information coordinator, share their experiences with the complexities of care coordination in patients with multisystem conditions such as HHT, particularly those who must travel a great distance for their care.

In this issue, you will learn that HHT is an inherited, autosomal dominant disorder of the TGF-ß signaling pathway that results in disordered angiogenesis. It is caused by mutations in gene coding for the membrane-bound receptors endoglin (ENG) and for intracellular SMAD4. This defective signaling presents multiple potential targets for precision therapeutics, including those associated with bone morphogenetic protein 10 (BMP10) and activin, A receptor type II-like 1 (ACVRL1), and for intracellular SMAD4. This discrete pathway presents multiple potential targets for precision therapeutics, bringing a cure within reach.

We welcome any suggestions or comments on how we might support you in the care of your patients. Please enjoy this issue of Respiratory Reader.

With great enthusiasm and respect,

Rama Mallampalli, MD
Professor of Medicine
Chief, Pulmonary, Allergy, and Critical Care Medicine
Director, Vascular Medicine Institute

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Hereditary Hemorrhagic Telangiectasia (HHT)

By Christopher Faber, MD

The incidence of HHT is estimated at one in 5,000. However, a large cause is receptor type II-like 1 (for the transforming growth factor-beta (TGF-ß) superfamily (7). The most several distinct genes, all of which are components of the signaling pathway. Disordered angiogenesis of HHT is caused by mutations in one of hypertension, or high-output heart failure (6,7). 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. Disordered angiogenesis of HHT is caused by mutations in one of the above-referenced genes. The remaining two criteria are unlikely to have HHT. 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.

HHT is now recognized as an autosomal dominant disorder of angiogenesis that results in vascular malformations of the skin, mucous 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 result in cirrhosis, portal hypertension, or high output heart failure (6,7).

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 systemic anticoagulation. In patients who continue to bleed after endoscopic treatment can be considered for systemic anticoagulation or chemoprophylaxis.

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, 16). Epistaxis is conveniently quantified using a tool called the Epistaxis Severity Score (16), which considers the frequency, duration, and severity of nosebleeds. Management of epistaxis involves the use of topical vasoconstrictors, systemic anticoagulation, and systemic antithrombotic agents. Epistaxis refractory to endoscopic treatment can be considered for systemic anticoagulation or chemoprophylaxis. In patients who continue to bleed after endoscopic treatment can be considered for systemic anticoagulation or chemoprophylaxis.

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-portal vein shunts, these patients can have profound exercise intolerance. 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 bile duct obstruction. Management of hepatic complications is largely with medical therapy for heart failure and portal hypertension. Embolectomy 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 (28). PAVM can cause hypoxemia (from right-to-left shunting) and neurovascular complications. Because blood flow 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 present, echocardiography is a CT scan is performed. If PAVM is found, 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 to recommendations for subacute bacterial endocarditis) for dental work. Also, they are advised to have 0.2 micron (0.2 µm) filters employed for any intraoperative therapy (to prevent paradoxical 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 specialist 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 (31). In summary, HHT is a rare disorder that frequently goes undiagnosed and can result in stroke, cerebral hemorrhage, or brain abscesses. 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. Optimal 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 PACC’s current publications and suggested readings for this issue, visit UPMCPhysicianResources.com/Pulmonology.
It is well established that heterozygous mutations in receptor-like kinase 1 (ALK1, which encodes the protein, ALK1), endoglin (ENG), and SMAD4 result in hereditary hemorrhagic telangiectasia (HHT) (S3), which is characterized by a predisposition to the development of direct connections between arteries and veins, or arteriovenous malformations (AVMs). However, how these proteins function within endothelial cells to establish and maintain normal arterial–venous separation remains unknown. My laboratory uses a zebrafish model of HHT to uncover the molecular and cellular errors that lead to AVMs.

Why Zebrafish?
Zebrafish embryos are an excellent model for studying vertebrate vascular development and HHT. These 2-mm long, optically transparent embryos develop rapidly, initiating heartbeat and circulation through a stereotypically patterned vasculature by ~26 hours post-fertilization. These attributes, combined with the ease of engineering fluorescent transgene expression to mark specific cell types, allow real-time imaging of vessel development at cellular resolution. Importantly, zebrafish vascular development is guided by the same molecular signals as human vascular development, including dependence on ALK1 signaling. zebrafish acvrl1 homozygous mutants invariably develop embryonic lethal high-flow cranial AVMs at ~40 hours post-fertilization (S4). Using this zebrafish model, we have made significant contributions to the understanding of the molecular mechanisms of ALK1 signaling, the natural history of HHT-associated AVMs, and the regulatory mechanisms controlling acvrl1 gene expression. Our goal is to use this knowledge to establish novel access points for development of HHT therapeutics.

New Components of the ALK1 Signaling Pathway
ALK1 is a transforming growth factor beta (TGF-β) superfamily type I receptor kinase/thrombospondin kinase that is predominantly expressed on the plasma membrane of arterial endothelial cells. Upon extracellular ligand binding to a molecular complex containing ALK1, a TGF-β family type II receptor and, endoglin, the type I receptor phosphorylates ALK1, and ALK1 then phosphorylates intracellular proteins SMAD1, SMAD5, or SMAD8. Phosphorylated SMAD1/5/8 binds to SMAD4, translocates to the nucleus, binds specific regulatory sequences within genomic DNA, and alters expression of associated genes. Using zebrafish genetics, we demonstrated that the critical ALK1 ligand during embryonic development is bone morphogenetic protein 10 (Bmp10); knockdown of bmp10 expression generates embryonic lethal ANAVIs identical to those that develop in acvrl1 mutants (S5). BMP10 is produced exclusively by the vertebrate heart and is detected in serum (5, 8), supporting the idea that ALK1 activation requires a circulating endothelium ligand.

The genes directly regulated downstream of BMP10/ALK1 phospho-SMAD are currently unknown. In zebrafish acvrl1 mutant arterial endothelial cells, we see loss of expression of the mRNA encoding the von willebrand factor, endothelin1, and increased expression of the mRNAs encoding the promotergnous chemokine receptor, Ccr4, and the Notch ligand, Dll4 (S, 9, 10). Although normalizing expression of these genes individually does not prevent AVM development (9, 10), it is possible that these changes in gene expression reflect an enhanced migratory and vasodilatory state that may be targeted for therapy.

Cellular Mechanisms of AVM Development
Although the genes responsible for 80 to 95 percent of HHT were identified 20 years ago (1, 2), we do not understand how ALK1 signaling influences endothelial cell behavior or why defects in ALK1 signaling lead to AVMs. Our analysis of AVM development in zebrafish acvrl1 mutants revealed that AVMs arise via a two-step process (9). In Step one, endothelial cell number and caliber increase in acvrl1-positive cranial arteries just upstream of the prospective shunt. This event is the direct result of acvrl1 loss-of-function and is phenocopied by loss of blood flow. In Step two, normally transient vessel segments are maintained between enlarged cranial arteries and draining veins. These segments progress to high-flow, embryonic lethal AVMs. This second step in AVM development is not genetically determined; acvrl1 mutants do not retain these vessel segments in the absence of blood flow.

Our two-step model of AVM development suggests that blood flow plays two distinct and opposing roles in AVM development. In wild type embryos, blood flow prevents AVMs by inducing both acvrl1 expression (see below) and ALK1 activity (via circulating Bmp10) to limit vessel caliber. In acvrl1 mutants, blood flow precipitates AVMs downstream of enlarged arteries (S, 9). Current studies are focused on defining how blood flow affects endothelial cell migration within the blood vessel wall and determining whether mechanical force and/or circulating factors mediate effects of blood flow on these two distinct steps of AVM development.

Control of ACVRL1 Gene Expression
Because HHT is an autosomal dominant disease caused by haplosufficiency, enhancing expression of the wild type copy of the disease gene may have therapeutic benefit. We discovered that in zebrafish, arterial endothelial cell acvrl1 expression requires blood flow (S9), and unpalliated work demonstrates exquisite sensitivity to both blood flow and intact Bmp10/ALK1 signaling at the level of transcription. These data suggest that Bmp10/Alk1 activity is required to maintain acvrl1 expression via positive feedback, but we cannot rule out roles for mechanical force or circulating factors in addition to Bmp10 in control of acvrl1 expression.

Toward Development of Targeted HHT Therapies
Current drug therapies available to HHT patients inhibit angiogenesis or enhance clotting, but none have proven effective in reducing bleeding over the long term or in reversing HHT pathogenesis (S10). As such, there is a pressing need to develop targeted therapeutics for HHT patients. Our research suggests several novel approaches. Based on the recent success of Bmp9 administration in reversing pathology in a haplosufficient mouse model of pulmonary arterial hypertension (S12), we propose that BMP10/Alk1 signaling may enhance signaling through wild type Alk1/Eng and thereby overcome haplosufficiency in HHT. Based on the changes in cell behaviors and gene expression associated with AVM development in our zebrafish model, we suggest that dampening arterial endothelial cell migration, limiting vasodilation, or manipulating mechanotransduction pathways may have therapeutic benefits in HHT. Finally, based on our finding that acvrl1 expression is regulated by blood flow in zebrafish, we postulate that enhancing this as yet undefined molecular regulatory pathway may increase ALK1 signaling beyond a threshold required to maintain normal vascular connections.

For a list of references to this article, other articles in this issue, and the Division of Pulmonary, Allergy, and Critical Care Medicine at UPMC, visit UPMPPhysicianResources.com/Pulmonology.
Case Presentation

Kate is a happy and active six-year-old with hereditary hemorrhagic telangiectasia (HHT). She was born borderline-preterm, delivered at 36 weeks gestational age. She had a large head circumference and skin telangiectasia were noted. Further evaluation demonstrated that Kate had congenital hydrothorax secondary to a grade II intraventricular hemorrhage (IVH) in utero requiring an intraventricular shunt. IVH is a common complication of early prematurity but not at Kate’s gestational age. Due to her unusual presentation, she was referred to a geneticist at nine months and her genetic screening tests at the evaluation were all normal. However, a significant family history of epistaxis was uncovered requiring, cauterization in her mother and maternal grandmother. In addition, the geneticist noted telangiectasia on both her mother’s and maternal grandmother’s tongue. At that time, molecular testing for HHT was sent that confirmed the suspected clinical diagnosis of HHT and that demonstrated a nonsense mutation; with a single change of C1757T/A in exon 12 of the endothelin (ENG) gene located at chromosome 9q34 locus resulting in “stop” (written as c.1757X5 or L472X).

Unfortunately, Kate was lost to follow up for four years. With the development of the HHT Center of Excellence at UPMC, Kate’s case was re-introduced to the multistep clinical screening process. The team of specialists, including radiologists, geneticists, and pulmonologists, examined Kate and ultimately, her diagnosis was confirmed. She was followed up by the HHT Center at UPMC, where she was referred to the center’s interventional radiologist, who assessed that none of the lesions warranted at this time.

Cerebral and pulmonary AVMs appear to be more commonly associated with mutations in the ENG gene. There are only a few reported cases of IVH due to cerebral AVMs in children. Therefore, Kate’s history of IVH at birth is highly suggestive that she had intracranial AVM which bled in utero even though her screening brain MRI/A were normal. She was evaluated by the HHT Center at UPMC for her telangiectasia. The team of specialists, including radiologists, geneticists, and pulmonologists, examined Kate and ultimately, her diagnosis was confirmed. She was followed up by the HHT Center at UPMC, where she was referred to the center’s interventional radiologist, who assessed that none of the lesions warranted at this time.

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Given that her primary symptom was epistaxis and that she was traveling a distance, we coordinated a visit with otorhinolaryngology and the medical director at which time the visit is planned. The patient we describe below will illustrate the importance of this coordination and care.

One of our very first patients was a 50-year-old woman who lived four to five hours away from Pittsburgh. She was referred by her local otorhinolaryngologist for epistaxis and telangiectases. Although she was referred by a specialist, we discovered that her insurance required a referral from her primary care physician in order for her visit to be covered. This highlights the importance of reviewing the patient’s insurance during the intake interview, particularly when it is a case not common to the area.

Referrals: Visit Planning and Care Coordination for the HHT Patient

Visit planning and care coordination are essential to properly and efficiently managing a patient with hereditary hemorrhagic telangiectasia (HHT). In our center, that planning and coordination is managed by the outpatient nursing coordinators and patient information coordinators. The success of this endeavor requires the coordinators to form collaborative working relationships with the patient, the referring practices, laboratory services, and the specialists within our own health system who are collaborating in the care.

When patients call to obtain information about our program, they are provided with a detailed overview of what our center offers. They undergo an intake interview focused on family history, symptoms, and screening for complications of HHT. Patients are advised to obtain all outside imaging and have any pertinent records forwarded to the office so that they are available at the time of their evaluation. Finally, due to regional variations in payer coverage, it is essential to evaluate the insurance coverage during the intake interview to be sure that all required referrals and authorizations are obtained. Once this information is collated, it is reviewed with the medical director at which time the visit is planned. The patient we describe below will illustrate the importance of this coordination and care.

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Given that her primary symptom was epistaxis and that she was traveling a distance, we coordinated a visit with otorhinolaryngology and the medical director on the same day. She reported a family history of epistaxis and stroke, and her examination revealed skin and tongue telangiectases.

Review of her outside studies, which she obtained upon our request, revealed the presence of a pulmonary arteriovenous malformation (AVM) and spinal artery aneurysms. Finally, at the end of the visit, we reviewed the findings of the visit, made plans for follow up care, answered all remaining questions, and provided educational material for the patient to review at her leisure.

She needed to have embolization of her pulmonary AVM and an evaluation of her intra-abdominal vascular anomalies. This patient, like most who travel a distance, preferred to have her consult and procedure scheduled as close together as possible. After communicating our findings with the primary care office and obtaining appropriate referrals, we coordinated a return visit for consultation with a vascular surgeon followed by embolization of her pulmonary AVM in the Interventional Radiology Division.

The time of this writing, her nosebleeds are under control with nasal hyegine, her pulmonary AVM has been embolized, and family genetic testing confirmed the presence of an HHT mutation. Given that she has children, she was advised to have them evaluated for HHT.

In conclusion, patients with confirmed or suspected HHT require efficient coordination of care to facilitate multidisciplinary evaluation and treatment. They require logistical support for travel planning and to negotiate their visit itinerary. They often require guidance to understand the rules and requirements of their health insurance coverage. Finally, they require education regarding how to manage their condition. At our center, the nurse coordinator and patient information coordinator provide these essential components to optimize patient experience and outcomes.