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The Division of Pulmonary, Allergy, and Critical Care Medicine at UPMC

SPRING 2016

In This Issue

BEST HOSPITALS U.S.News & WORLD REPORT PULMONOLOGY 2015–16

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 of 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 (BMP 10) in the pathogenesis of arteriovenous malformations.

Dr. Suneeta Madan-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 experience 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 inheritable, autosomal dominant disorder of the TGF-ß signally pathway that results in disordered angiogenesis. It is caused by mutations in gene coding for the membrane-bound receptors endoglin (*ENG*), 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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UPMC LIFE CHANGING MEDICINE

Hereditary Hemorrhagic Telangiectasia (HHT)

By Christopher Faber, MD

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-ß) 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 TGB-ß 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 *RASA 1* (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 or 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 otolaryngologists with expertise in HHT for treatment. Improved and sustained control of epistaxis is obtained by combining laser ablation with injection of bevicizumab (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).

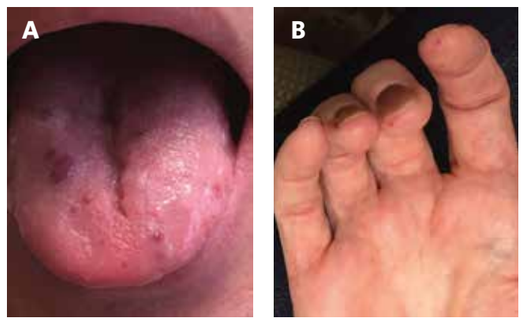

Figure 1. *Typical telangiectaes of HHT noted on tongue (A) and hands (B).*

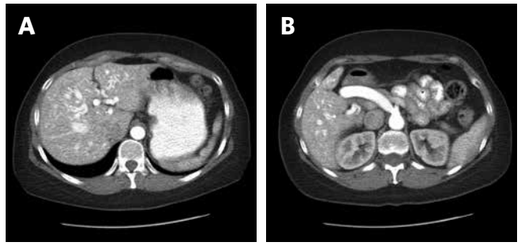

Figure 2. *Arteriovenous malformations of the liver (A) resulting in hypertrophy of the hepatic artery (B).*

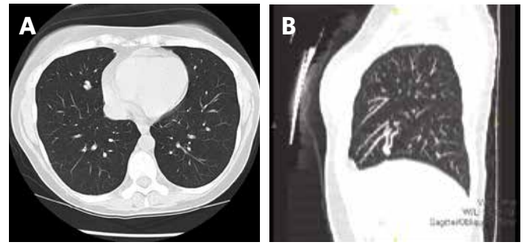

Figure 3. *Small pulmonary AVM in right middle lobe on the transverse section CT images (A). Note that the feeding artery and draining vein are better seen on the sagittal reconstruction images (B).*

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 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.

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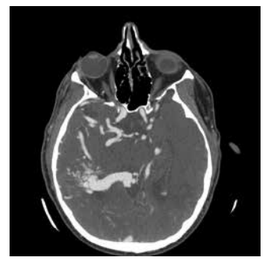


Figure 4. *Right temporoparietal AVM in a patient with HHT. There is a large dilated vein draining the AVM traversing the right lateral ventricle atrium into the vein of Galen.*

Lab Spotlight: Using Zebrafish to Understand the Mechanism of HHT Pathogenesis

By Beth Roman, PhD

It is well established that heterozygous mutations in activin receptor-like kinase 1 (*ACVRL1*, which encodes the protein, ALK1), endoglin (*ENG*), and *SMAD4* result in hereditary hemorrhagic telangiectasia (HHT) (1-3), 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.

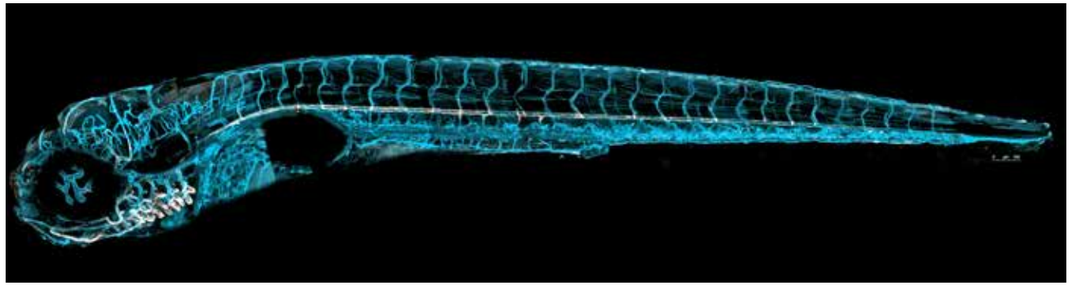
Why Zebrafish?

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 (4). 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 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-ß) superfamily type I receptor serine/threonine 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-ß family type II receptor, and endoglin, the type II receptor phosphorylates ALK1, and ALK1 then phosphorylates intracellular proteins SMAD1, SMAD5, or SMAD8. Phosphorylated SMADS 1/5/8 bind to SMAD4, translocate to the nucleus, bind specific regulatory sequences within genomic DNA, and alter 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 AVMs identical to those that develop in *acvrl1* mutants (5). BMP10 is produced exclusively by the vertebrate heart and is detected in serum (5-8), supporting the idea that ALK1 activation requires a circulating endocrine 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 vasoconstrictor, endothelin-1, and increased expression of the mRNAs encoding the promigratory chemokine receptor, Cxcr4, and the Notch ligand, Dll4 (5, 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.



Two-photon image of transgenic 5-day old zebrafish with all endothelial cells blue and alk1*-positive endothelial cells gray/orange. Lateral view, head is to the left.*

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 deficits 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 drainage 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 (5, 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.

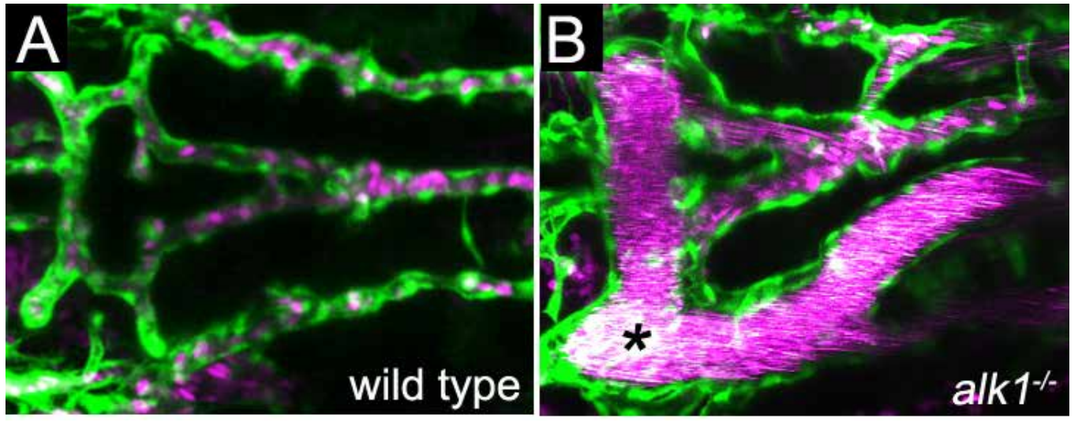
Control of ACVRL1 Gene Expression

Because HHT is an autosomal dominant disease caused by haploinsufficiency, 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 (9), and unpublished 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 (11). 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 rescuing pathology in a haploinsufficient mouse model of pulmonary arterial hypertension (12), we propose that BMP10 ligand therapy may enhance signaling through wild type ALK1/ENG and thereby overcome haploinsufficiency 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 PACCM's recent publications and suggested readings for this issue, visit UPMCPhysicianResources.com/Pulmonology.



Dorsal cranial vasculature in 2-day old wild type (A) and alk1 *mutant (B) zebrafish. Endothelial cells green, red blood cells magenta. Asterisk marks AVM in* alk1 *mutant.*

Case Presentation

By Suneeta Madan-Khetarpal, MD

Jessica Sebastian, MS, LCGC

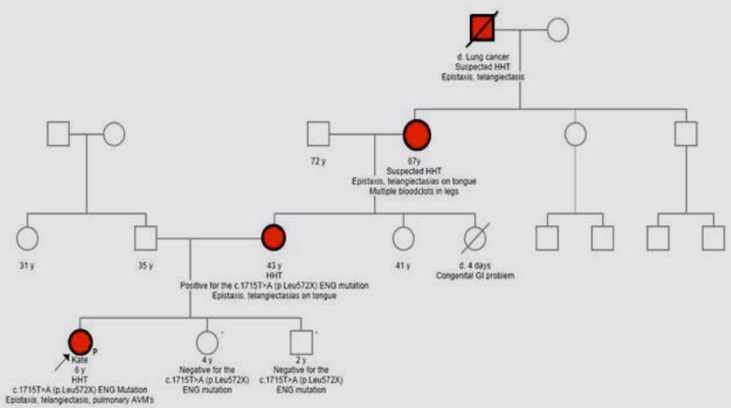
Andrew McCormick, MD

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 a skin hemangioma at birth. Further evaluation demonstrated that Kate had congenital hydrocephalus secondary to a grade III 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 at c.1715T>A in exon 12 of the endoglin (ENG) gene located at chromosome 9q34 locus resulting in "stop" (written as p.Leu472X 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 recovered and the family was re-introduced to the multistep clinical screening process. A team of physicians, specializing in HHT, has worked to ensure that Kate receives the best in HHT preventative and cutting edge care. Kate was evaluated by the HHT Pediatric Center's diagnosticians to characterize the extent of her ear nose and throat (ENT), pulmonary, neurologic, and gastrointestinal involvement. Her ENT evaluation demonstrated the development of intermittent epistaxis, treated with humidification and intranasal saline. She now is followed by the HHT Center's ENT expert to monitor and manage complications as this disease progresses.

Kate underwent pulmonary screening with a contrast transthoracic echocardiogram, which demonstrated delayed presentation of saline bubbles into the left atrium after five cardiac cycles, suggestive of a possible AVM. Kate then underwent a CT angiogram of her chest which demonstrated four tiny AVMs within her lung parenchyma. Her case was reviewed by the HHT center's interventional radiologist, who assessed that none of the lesions were of a clinically significant size to require coiling. She will require close observation to check for the progression of these lesions, antibiotic prophylaxis to prevent possible intracranial "seeding" that could result in brain infections during elective procedures, and filtered IV solutions to prevent air bubble embolization. Finally, Kate's blood picture shows that she is normocytic with age appropriate hemoglobin as well as iron stores and has no history of bloody stools. Therefore, no further gastrointestinal screening is warranted at this time.

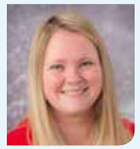
Cerebral and pulmonary AVMs appear to be more commonly associated with mutations in the ENG gene. There are only a few reported cases of IVH due to cerebral AVMs in children. Therefore, Kate's history of IVH at birth is highly suggestive that she had intracranial AVM which bled in utero even though her screening brain MRI/MRA demonstrated no specific lesions of HHT at this time. Going forward, the HHT team at UPMC will work to individualize Kate's care to ensure she stays healthy throughout her life. Due to her unfortunate presentation, her family members have been identified as HHT gene carriers and now will receive the appropriate screening and care in our adult HHT Center of Excellence.



At least four generations are afflicted by HHT. The diagnosis of HHT unveiled and brought to surface by our 9 month old Kate, the proband is shown by the arrow. Please see the intra-familial variability of HHT. The two siblings tested negative and do not warrant surveillance for varied manifestations of HHT.

Referrals: Visit Planning and Care Coordination for the HHT Patient

By Jessica Romanias, BSN, RN



Melody Porter

Kathy Lindell, PhD, RN

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 nurse 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.

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 otolaryngologist 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 carrier not common to the area.

Given that her primary symptom was epistaxis and that she was traveling a distance, we coordinated a visit with otolaryngology 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 splenic 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.

At the time of this writing, her nosebleeds are under control with nasal hygiene, 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.