[Internal Medicine Grand Rounds]

HEREDITARY HEMORRHAGIC TELANGIECTASIA

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HISTORY

Hereditary epistaxis was first described in 1864[115], though neither that nor Babington's description a year later report an association with telangiectasia.[6] These reports were not generally recognized; nor were subsequent descriptions of telangiectasia, hereditary transmission, and epistaxis by Legg[69] in 1876, or a similar kindred reported by Chiari in 1887.[15] The first widely recognized connection of epistaxis to telangiectasia was made by Rendu in 1896.[101] Osler added three cases, and recognized familial occurrence in 1901.[83] Weber elucidated the familial nature and lack of coagulation abnormality, and thus earned his eponymic association.[123] By precedence of description, this eponym should be Rendu-Osler-Weber (and is generally preferred in Europe, particularly France), even though Osler-Weber-Rendu is the most common usage here. Hanes was responsible for naming the syndrome hereditary hemorrhagic telangiectasia, the designation now most often preferred, in 1909.[52]

Pulmonary arteriovenous malformations (PAVMs) were first described relatively recently in medical history; Churton reported the autopsy findings in a young boy with cyanosis in 1897.[17] PAVMs were first diagnosed during life in 1939.[113] As in many later cases, clubbing and polycythemia were present in a 40-year-old man. Based on the correlation of physical with postmortem findings, the triad of cyanosis, clubbing, and polycythemia was identified with PAVM in 1932.[95] Hereditary hemorrhagic telangiectasia (HHT) was first connected to pulmonary arteriovenous malformation in 1938.[103]

Publications (and understanding) of HHT remained largely descriptive until the late 1970's. The perfection of catheter-based therapy of PAVMs by White and Terry[118] led to a large number of patients being referred to Johns Hopkins. It became apparent that most patients referred had HHT, whether or not the referring doctor was aware of the diagnosis. Unable to find colleagues interested in providing longitudinal care for these patients, White (trained as an internist on the Osler service before entering interventional radiology) opened a clinic. His growing patient population and leading-edge expertise led directly to the elucidation of the genetics of the disease, the creation of the HHT Foundation International, the founding of the Global Research and Medical Advisory Board, HHT Foundation International, and the development of centers of excellence in the diagnosis and management of HHT, now numbering 14 in the North America and 18 in Europe and Asia.

GENETICS

HHT is an autosomal dominant disease. Its frequency was believed until relatively recently to be fewer than 3 per 100,000 people. [121] Newer studies suggest a much higher prevalence. The highest frequency reported, 1:1,331, occurs in the Afro-Caribbean population of the Netherlands Antilles, presumably due to a founder effect. [124] Other estimates vary geographically; 1:6410 in Denmark,[63] 1:8,000 in Japan [21] and 1:16,500 in Vermont. [49] Phenotypic variation is extreme, ranging from asymptomatic to severely symptomatic, and from cases with no or few mucocutaneous lesions to those with diffuse cutaneous telangiectasia. For many patients, the disease remains undiagnosed by their primary care physicians, suggesting that disease frequency may be greater than reported, and that some patients with "isolated" PAVMs may actually have HHT.

A gene for HHT was first localized to chromosome 9, region q^{33-34} ($9\ q^{33-34}$). [56, 79, 108] Investigation revealed the protein product to be endoglin, which associates with different signaling receptors and can modify TGF-beta-1 signaling.[75] The same work showed the disease to be genetically

heterogeneous, with multiple mutations in the responsible gene. It rapidly became clear that there were other chromosomal mutations resulting in the same syndrome, and the endoglin mutation disease was designated HHT-I; it was noted to be associated more often with PAVMs than were those with non-9q[3] mutations, [8,76,88] and has cerebral AVM's more frequently than other genotypes. A haploinsufficient mouse model also demonstrated phenotypic heterogeneity which was very dependent on the genetic background. [12]

The activin receptor-like kinase 1 gene (ALK-1 or ACVRL1) on chromosome 12 is the second locus for hereditary hemorrhagic telangiectasia.[10,61] It produces a transforming growth factor (TGF)-beta superfamily type I receptor. Mice heterozygous for a loss-of-function mutation in ALK-1 develop age-dependent vascular lesions in the skin, extremities, oral cavity and in the lung, liver, intestine, spleen and brain, similar to those seen in HHT patients, [114] who have hepatic AVM's and their complications more frequently than those with the endoglin mutation. Nevertheless, it is not possible to distinguish between the two mutations in any given patient without genetic analysis. Disease resulting from mutations in this gene has been designated HHT-2. Endoglin, ALK-1 and Smad4 proteins modulate signaling by the transforming growth factor (TGF)-beta superfamily, ligands for which include TGF-betas, activins, inhibins and bone morphogenetic proteins (BMPs).

A small number of patients with juvenile polyposis also have hereditary hemorrhagic telangiectasia. This appears to be due to mutations in MADH4 (SMAD4); SMAD proteins influence the cellular response to TGF-beta. [35, 36]

A fourth gene abnormality producing clinical HHT in a family on has been described on chromosome 5. The gene product is as yet unidentified. [18]

A fifth gene abnormality in a family with HHT has been described on the short arm of chromosome 7. [9] The gene product of this mutation is also unknown at present.

Most HHT appears to be caused by mutations in endoglin and ALK-1. Mutations can be identified in up to 88% affected individuals; [70,106] in one series, 61% were in endoglin, 37% in ALK-1, and 2% in MADH4. [92] ALK-1 mutations appear to be more common in France and Italy, with endoglin mutations more frequent in northern Europe and North America.[32,70,71]

The homozygous form of HHT appears to be lethal, resulting either in miscarriage or neonatal death, associated with explosive growth of mucocutaneous telangiectasia and diffuse PAVMs.[28,51]

PATHOPHYSIOLOGY

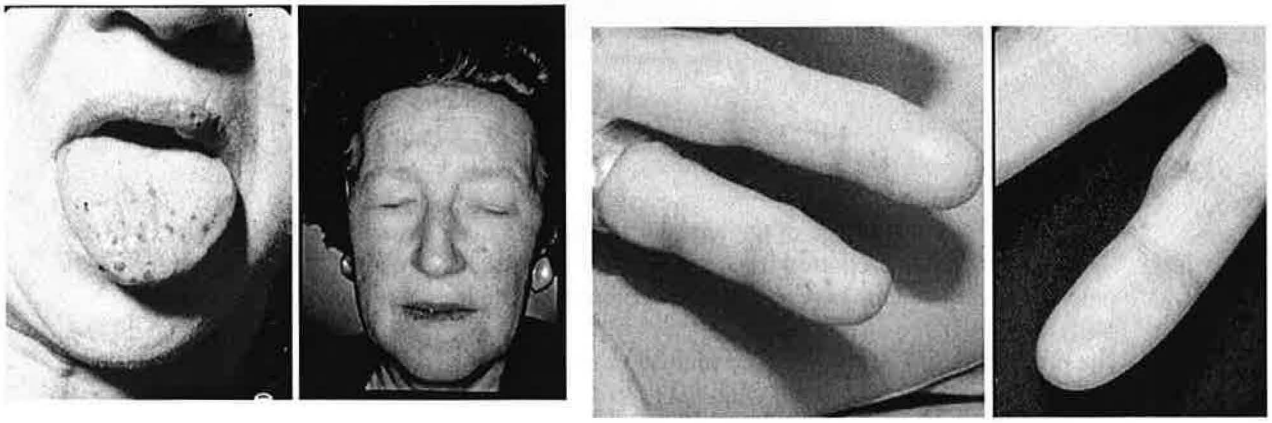
Disease manifestations are generally related to development of abnormal vessels. Telangiectasia are found on the skin and mucous membranes, including conjunctiva, lips, and tongue, as well as the GI tract. Arteriovenous malformations are generally responsible for symptoms arising in the lungs, central nervous system, and liver. However, the pulmonary hypertension associated with ALK-1 mutations likely has its genesis in altered ligand interaction with BMP's. The role of increased levels of circulating TGF-beta and VEGF, and the local over-expression of endothelial TPA is unclear.

CLINICAL PRESENTATION

Mucocutaneous

Telangiectasia vary widely in number among those with HHT, but have a characteristic appearance and distribution. They tend to occur on the outer helix of the ears, the malar eminences, the

lower lip, and the distal tongue, as well as the digits. They may also occur on the soft palate, the bulbar conjunctivae, and the palms. They rarely occur on the proximal arms or the trunk; most individuals reporting truncal telangiectasia are mistakenly identifying cherry hemangiomata. They rarely bleed, and are generally painless, though we have seen exceptions to both rules on the lower lip and digits. They often increase in size and number with age, and cutaneous telangiectasia are seldom identifiable until the second or third decade.[85] We have been struck by the frequency with which classic tongue and lip telangiectasia have been passed off as nonspecific blemishes by primary care physicians.



Mucocutaneous telangiectasia

Epistaxis

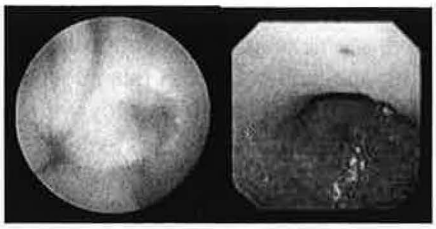
Epistaxis is the most common manifestation of HHT. Many references cite a prevalence of more than 95%. Our experience is somewhat different – prevalence in the population seen at Washington University was 227/292 (78%), and in part age-dependent. The mean age at onset of epistaxis in HHT is 12 years, with 54 percent of patients presenting by age 10. Severity ranges from very mild to life-threatening. [5] Anti-platelet agents almost invariably worsen nosebleeds, and most patients have learned to avoid aspirin by the time of presentation. Iron-deficient anemia is present in a minority of patients (94/292 [34%] at Washington University), and due most often to GI blood loss combined with epistaxis.

Nasal telangiectasia before and after laser photcoagulation

Gastrointestinal

The prevalence of telangiectasia in the GI tract is unknown, as asymptomatic patients do not ordinarily undergo screening endoscopy. It is likely very high. In symptomatic patients, telangiectasia predominantly involve the stomach and small bowel; bleeding from colonic telangiectasia is uncommon. In the Washington University cohort, GI blood loss of variable severity occurred in 65/292 (22%), similar to other series.[42] Symptomatic GI blood loss generally begins after age 40. Our group recognized a

syndrome of increased GI blood loss and epistaxis occurring in conjunction with increased cardiac output due most often due to hepatic AVM's.[131]



Gastrointestinal telangiectasia

Pulmonary

Estimates of the percentage of patients with HHT who have associated PAVMs have varied widely. Various series have reported frequencies of 15 percent,[14] 20 percent,[96] 24 percent, [77] 33%, [50] 49%, [20] and 57 percent. [45] Our experience is consistent with the higher numbers.

The proportion of PAVMs that are multiple has been reported to be approximately one-third;[96] multiple PAVMs are highly associated with HHT.[14]

The occurrence and frequency of symptoms related to PAVMs depend on how the patients are found—that is, whether they present with manifestations of disease or whether they are discovered as a result of screening. The asymptomatic state is most common when screening is the method of detection, with an incidence typically between 25 and 59%.[14, 24, 109, 112]

The age at onset is usually in the third or fourth decade.[85] The mean age at detection in various series is remarkably constant at 38 to 40 years. [14, 24, 41, 117] In one series, the patients ranged in age from 5 to 76 years, with a mean of 36; 26 percent presented at an age less than 21 years. [126] PAVMs are, however, uncommon in childhood; only 4 percent of affected persons are under 10. [44, 111)]

25-58% of patients are asymptomatic.[109] Pulmonary symptoms include dyspnea on exertion, with a frequency ranging from 27 to 71 percent. [23, 24, 109, 126] Platypnea and orthodeoxia also may occur. Hemoptysis ranges in frequency from 4 to 18 percent. [23, 109, 117, 126] Extrapulmonary symptoms include chest pain in 6 percent [25]. Physical signs due to the PAVM itself are relatively uncommon. As many as 25 percent of patients may exhibit no findings at all. [23] Hypoxemia, when present, is secondary to the right-to-left shunt, and may result in cyanosis and secondary polycythemia. This tends to occur in advanced disease, and has been reported in 9-73% (mean 30%).[7, 23 109] The frequency of clubbing has been reported in an average of 32 percent [109]; it is much less common in our experience. [23,42] Clubbing is nearly always associated with cyanosis. Clubbing may resolve after the PAVM is removed [41] or occluded. A pulmonary bruit, which is often described, is also variable; its frequency, probably influenced by selection bias, ranges from less than 10 percent to 58 percent. [7, 23, 24, 109] The severely affected person may have arterial hypoxemia at rest; those less severely affected may have orthodeoxia documented by supine and upright arterial blood gases.[125] Arterial blood gases, determined on blood samples drawn while the patient is breathing room air, followed by 100 percent oxygen, may reveal a significant right-to-left shunt. [44]

Significant hemoptysis occurs in fewer than 10 percent of patients; in our most recent series, it occurred in 5 of 142 (<4%). 2 of 5 occurred during pregnancy.[42] It may be massive and life threatening. Bronchial telangiectasia may be the cause, [14] but all cases in untreated patients in our experience have

been due to PAVMs. An increasingly frequent problem in recent years is hemoptysis following extensive embolotherapy after a delay of months to years. This has generally been due to post-embolization bronchial arterial collateral formation.

Hemothorax has been reported in up to 9 percent of patients,[126] but is usually less than 2%.[109] Pregnancy may cause PAVMs to enlarge, and has been associated with hemothorax on several occasions.[31, 38, 66] Hemothorax may also occur without any other predisposing factors, presumably caused by rupture of large subpleural PAVMs into the pleural space.[22]

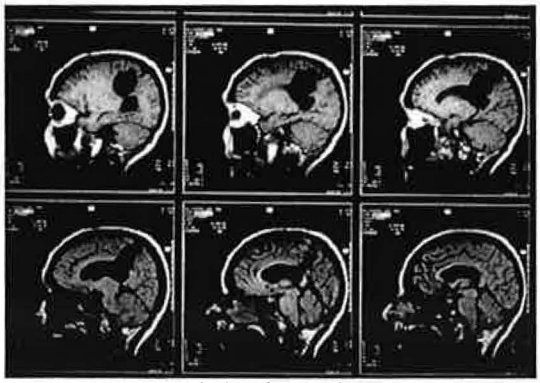
Pulmonary hypertension is uncommon.[120] Patients with PPH in HHT have ALK-1 mutations rather than mutations in the bone morphogenetic protein receptor type II (BMPR2) gene.[1]

Central Nervous System

The pulmonary capillary vascular bed appears to be an important filter for otherwise asymptomatic small emboli, and may also have a significant role in cleansing the bloodstream during transient bacteremia. Most neurologic complications, which occur in 8 to 12 percent of patients with HHT, are complications of PAVMs. In one series, 60 percent were due to PAVM, including brain abscess, paradoxical embolus, and hypoxemia.[85, 104]

Transient ischemic attacks occur in approximately 37 percent of patients with PAVMs.[126] PAVMs can cause symptomatic cerebrovascular accidents; the frequency of this complication ranges from 6 to 27 percent.[23, 109, 126] In our clinic, 28 of 132 patients screened by MRI had evidence of prior paradoxical embolic stroke.[42] Unfortunately, paradoxical embolization to the brain may be the first manifestation of an occult pulmonary venous malformation. This has been a particularly regrettable repetitive problem in young women taking oral contraceptives while smoking.

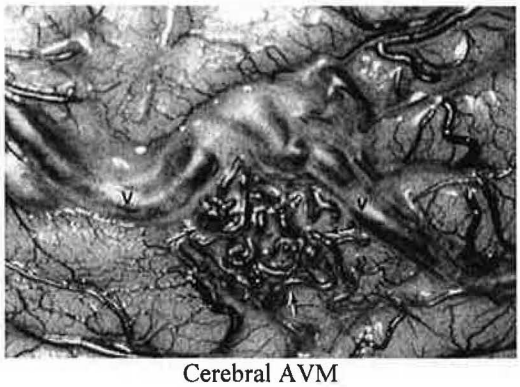
Brain abscess occurs in 3 to 10 percent of patients with PAVMs.[26, 109] In a series in our clinic, 5/132 (4%) had prior brain abscess.[42] Up to 1 percent of HHT patients may have brain abscesses (1000 times the incidence in the general population). In one series, 5 of 31 patients had recurrent abscess;[91] in another, 6 of 128.[37] Up to 8 percent of brain abscesses in the general population may be due to PAVMs.[39] Unfortunately, brain abscess may also be the first symptom of an occult PAVM, and many years may elapse before diagnosis of PAVM. Most occur following dental work. For that reason, antibiotic prophylaxis following the standard American Heart Association protocol for prevention of endocarditis is recommended.



Porencephaly after brain abscess

Migraine is more common in HHT than in the general population, and appears to be more common in those with PAVM. In one series, migraine occurred in 88 patients with HHT, a prevalence of 16.4%. The prevalence of migraine in patients with PAVM was 21.2%, which was significantly higher than in patients without PAVM (13.3%).[89] In our experience, migraines occurred in 74/292 (25%) with HHT. [42]

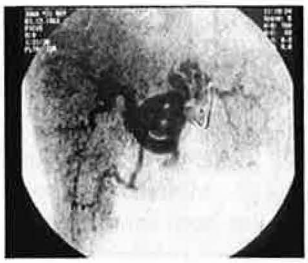
Cerebral arteriovenous malformations (CAVM's) occur in 4-8% of patients with HHT [33, 126] and tend to run in families.[60] Although CAVM's are not complications of PAVM's, they occur more frequently in patients with endoglin mutations, as do PAVMs. In our series of 149 patients screened by MRI, 11 had CAVM (7%). An additional 16 (11%) had telangiectasia or venous angioma (11%). [42] Although some have argued that the complication rate does not warrant routine screening, [74] the hemorrhage rate in individuals with cerebral AV malformations appears to be 1.4-2.0% annually, comparable to figures in the non-HHT population with cerebral AV malformations. [27] More recent data based on population screening is more favorable, in the range of 0.5% annually.[142]



Cerebral AVM

Hepatic

AVMs may also occur in the liver. The frequency is not clear; reported incidence ranges widely. The most reliable data suggests that about 40% have hepatic AVM's detectable by Doppler ultrasound.[143] The most common manifestation is high-output heart failure. This may result in pulmonary hypertension associated with elevated left-ventricular end-diastolic pressure; this must be differentiated from primary pulmonary hypertension. During a 9-year period between 1997 and 2006, 346 patients with HHT were evaluated at the Washington University HHT center. Of these patients, 17 (4.9%) were found to have high output cardiac state - 13 due to hepatic AVM's. [42] Other presentations include manifestations of portal hypertension, such as ascites or variceal bleeding, and manifestations of biliary disease, such as an elevated alkaline phosphatase level and abnormalities on bile duct imaging. [34] Ischemia related to shunting may result in noncirrhotic fibrous nodules (telangiectasia-associated hepatic fibrosis or "pseudocirrhosis"). [19, 105] On rare occasions, this may result in liver failure. In one series, hepatic AVM occurred in 17% of patients with ALK-1 mutations.[78] Liver transplantation may be life-saving. [11, 47]



Hepatic AVMs

CLINICAL DIAGNOSIS

The clinical diagnosis of HHT is based on the criteria developed at the international consensus conference in Curacao.[107] These include 1) epistaxis; 2) characteristic telangiectasia; 3) visceral involvement (GI telangiectasia or AVM's, AVM's of lung, liver, brain, or spinal cord); 4) characteristic inheritance pattern. Those with 3 or 4 criteria are considered to have definite HHT; those with 2, possible HHT; and those with 1 or 0 are considered unlikely to have HHT. It must be remembered that these criteria were developed to allow assignment of certainty for epidemiologic purposes, and not to substitute for clinical judgment. Children, in particular, are likely to have only one or two criteria even when they have HHT. Similarly, an adult with several pulmonary AVM's and a positive family history is very likely to have HHT, even in the absence of characteristic telangiectasia and nosebleeds.

EVALUATION OF PROBANDS WITH HHT AND SCREENING RELATIVES FOR HHT

The best approach to screening is a subject of considerable discussion in the literature, and the approach at HHT centers of excellence varies somewhat. An attempt to standardize an approach to screening and treatment was the subject of a recent consensus conference.[130] The discussion that follows will summarize the evidence for various screening tests, and will be followed by a description of the approach at the University of Texas Southwestern HHT Center.

A history and physical examination is conducted, focusing on Curacao criteria 1, 2, and 4. Evidence of GI and liver involvement is also sought during the exam. CBC is obtained for anemia evaluation. Careful screening for pulmonary and cerebral involvement is done, as detection in the asymptomatic patient may lead to prognosis-changing treatment. Intensive investigation to detect asymptomatic liver and GI involvement is not done, as there is currently no treatment that will alter the natural history of the disease if applied early.

Pulmonary AVMs - The severely affected person may have arterial hypoxemia at rest; those less severely affected may have orthodeoxia documented by supine and upright arterial blood gases.[125] Arterial blood gases, determined on samples drawn while the patient is supine and upright, have been advocated for screening. [125] However, this technique has not proved useful. Various combinations of shunt measurement utilizing albumin microspheres labeled with technetium-99m, PaO2 on room air, shunt measurement in subjects breathing 100% oxygen, and erect oxygen saturation measurement have been utilized, but all have insufficient sensitivity, specificity, or both.[44, 64, 84, 119, 129]

The reported sensitivity of chest radiographs varies widely, depending on whether they are used for screening or in patients with symptomatic disease. Rates of abnormality on the chest radiograph range from 41 [112] to 100 percent. [23] In our experience, chest radiography does not reliably detect PAVMs less

than 20 mm in size, and it may miss larger PAVMs when they are located in radiographically inopportune places, such as the costophrenic sulci, the retrocardiac region, or the proximal hila. [46]

The sensitivity and specificity of chest CT are unknown, although this modality appears to be more sensitive than are chest radiographs. [125] One early study suggested that CT enabled identification more than 98% of PAVMs and was superior to pulmonary angiography. [98] CT has also been advocated for pre-therapy planning. [97] Our experience has been somewhat less favorable; among 15 patients with CT's showing PAVMs, 20% had PAVMs missed, representing 42% of PAVMs in those patients. CT's interpreted as negative were falsely negative in 6 of 9 patients, representing 10 PAVMs. [45]

Gradient-echo MRI shows promise, but it can mistake tumors for PAVMs.[25] Gadolinium contrast-enhanced pulmonary magnetic resonance angiography (CEMRA) detected 79% of PAVMs found by helical CT, and all of those with a feeding artery diameter of at least 3 mm (i.e., PAVMs with clinical consequences). [62]

Echocardiography, using indocyanine green as a contrast material, was found to be effective in the diagnosis of intrapulmonary shunt, with delayed appearance of the contrast material in the left side of the heart.[110] This was rapidly improved by the use of agitated saline as contrast.[55] The intrapulmonary nature of the shunt can be determined by the delay, averaging four to five cardiac cycles, of left heart contrast appearance; when the echo is performed transesophageally, the region of a radiographically undetectable PAVM may be inferred by the appearance of contrast in one or another pulmonary vein. If contrast echocardiography is negative, a PAVM is very unlikely, and an alternative cause of the pulmonary nodule should be sought. On rare occasions, if the PAVM is fed by a systemic artery, the contrast echocardiogram will be negative, and pulmonary angiography should be undertaken if suspicion is high. If the contrast echocardiogram is positive, the definitive test is pulmonary angiography. Angiography is 100 percent sensitive in our experience, with correct application of the appropriate views, for vessels of 2 mm or more. However, experience elsewhere has not always been concordant with ours (vide infra).

Contrast echocardiography is more sensitive than symptoms, plain radiography, measurements of SaO2, PaO2 on room air, and PaO2 breathing 100 % oxygen..[20, 64] . It is positive in 55-73% of patients.[42, 84] and may be the only positive screening study in 31% of patients. [81] Up to 80% will have persistently positive contrast echo findings after undergoing embolotherapy. [67] In patients with diffuse small PAVMs or telangiectasia, transephogeal contrast echocardiography may provide the definitive evidence. [82] Based on the above information, a screening algorithm based on contrast echocardiography and anteroposterior chest radiograph, followed by chest CT if either test is positive, is used in many centers. [20] This algorithm is based on studies in which CT without contrast was used as the "gold standard", with confirmatory pulmonary angiogram only if positive.

However, our group has for many years followed a scheme in which patients with HHT are screened with saline contrast echocardiography. Those with positive findings undergo pulmonary angiography. This approach identified PAVMs in 57% of patients screened. In combination with our observations regarding false-negative chest CT, we believe the frequency of PAVMs identified, greater than in any other series justifies this approach. In ~15% of patients with angiographically detectable PAVMs using this approach, no therapeutic embolization results. These PAVMs represent an opportunity to more fully understand the natural history and complication rates of PAVMs. [45]

Technology is having an impact on this approach. 64-row multi-detector array chest CT with reconstruction is under evaluation as an alternative to angiography. Preliminary results in more than 60 patients suggests that this technique is at least equivalent to pulmonary angiography.

Cerebral AVMs - Cerebral magnetic resonance imaging (MRI) is currently the most sensitive non-invasive test, although it will fail to detect a significant proportion of AVMs. [33] CT angiography is currently being investigated as an alternative.

Genetic testing – Each proband with definite HHT is offered genetic testing. If a disease-causing mutation is identified, screening is recommended for all first-degree relatives.

TREATMENT

Epistaxis – For mild bleeding, local pressure and nasal hygiene may suffice. Ambient air should be adequately humidified. Nasal saline douches may aid and will help remove crusts. Topical ointments can help maintain mucous membrane moisture. If allergic rhinitis increases bleeding, nasal steroids may be useful. If bleeding is more troublesome, topical treatment with antifibrinolytics (pharmacy-compounded tranexamic acid spray) or estrogen (Premarin cream) may help. Iron supplementation, either orally or IV, is necessary for treatment of iron-deficiency anemia. For more severe bleeding, systemic therapy with estrogens or anti-fibrinolytics (epsilon aminocaproic acid or tranexamic acid) should be given only after investigation of treatment for pulmonary AVMs, as increased coagulability may result in paradoxical embolism. Prospective studies of estrogens and tranexamic have been disappointing, with neither favorably affecting hemoglobin and only the latter reducing nosebleeds by patient report.[146, 147] Embolization therapy may substantially reduce bleeding, but is not durable, and has fallen out of favor.[144, 145] Surgical therapy is reserved for the most severe cases, and include laser photocoagulation, septal dermoplasty, and Young's procedure (nares closure).[136-141] The latter two should be performed by ENT surgeons with extensive experience. Based on positive impact on angiogenesis in mice, thalidomide is in clinical trials in the U.S.[134, 135] Raloxifene, a selective estrogen receptor modulator, has recently been designated an orphan drug in Spain on the basis of preliminary studies. Further clinical trials are anticipated. Recent reports have suggested a role for topical or systemic bevacizumab (Avastin).[132, 148,149] We anticipate commencement of a clinical trial of topical bevacizumab within the year.

Pulmonary AVMs - Early treatment of PAVMs consisted of thoracotomy and resection. The first successful surgical approach was pneumonectomy, reported in 1942.[54] As thoracic surgery improved, the extent of surgery diminished; by 1959, local excision was the procedure of choice. [14] Surgical removal of a PAVM inevitably results in loss of viable lung tissue, a problem for patients with multiple PAVMs; the record is probably held by a patient who underwent staged bilateral thoracotomies with removal of 23 PAVMs, with substantial symptomatic improvement. [13] Thorascopic resection has recently been described. [122] Although surgical mortality can be as low as 0%, [14] the general anesthesia, morbidity of thoracotomy, and loss of viable lung tissue made a new approach desirable.

Embolization of PAVMs has proved to be an excellent alternative. This procedure was first performed using homemade coils. The procedure was refined and perfected at Johns Hopkins by Terry, White, and colleagues. [118] The original procedure utilized silicone balloons unless the feeding vessel was larger than 9 mm in diameter, in which case embolization coils with thrombogenic Dacron tails were used. [126] Currently, the choice of coil vs. balloon generally reflects PAVM size, operator preference and center experience. Recently, Amplatzer vascular closure devices have become the method of choice for several centers, though not all have adopted. Generally, all PAVMs with feeding vessel diameter of 3 mm or larger are embolized. Results have been very good, with success rates greater than 93%, [4, 90] and embolization therapy is now the procedure of choice, with an apparent mortality of 0%, few serious complications, no loss of pulmonary parenchyma, and no exposure to anesthesia or thoracotomy. Pregnant women requiring urgent embolotherapy because of hemoptysis or hemothorax may safely undergo embolization, with radiation exposure to the fetus acceptable after 16 weeks of gestational age,

with successful pregnancy outcome. [40] Embolotherapy may also be performed safely and effectively in children.[30]

There are some limitations. The feeding vessel must be 2 to 3 mm in diameter or larger. It is technically feasible to embolize most PAVMs, but occasionally this is not possible. All but three patients in our 18-year experience have been able to be treated with embolotherapy (2/132 in the most recent series). [42] A majority will have persistent intrapulmonary shunt and should receive pre-dental antibiotic prophylaxis. [67]

Recanalization of the embolized vessel may occur. [73, 80, 99, 100] Rates of 2-8% have been reported. [87, 128] This may require repeated embolotherapy, and it has been suggested that follow-up by CT occur at one month and one year.[128]

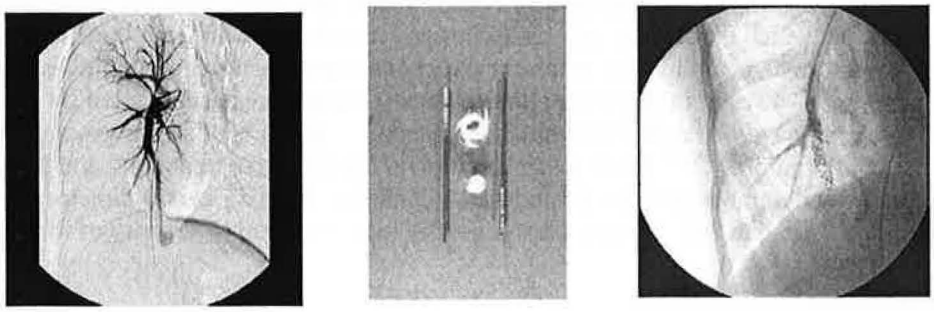
While observations documenting serial growth of small PAVMs are somewhat limited, there is published evidence to support their growth with time. [23, 58, 73, 87, 121, 128] Progression of PAVMs appears more likely in those with multiple PAVMs.[112] It has been suggested that patients with treated PAVM need follow-up every 5 years to detect growth of small PAVMs that could become large enough to cause paradoxical embolization and stroke. [128]

In general, successful embolization of most or all visible PAVMs results in abatement of hypoxemia and its complications, [16] but a small number of patients have diffuse small PAVMs not amenable to embolization.

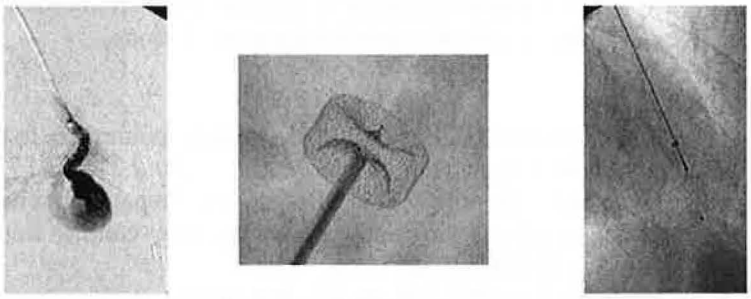
Occlusion of all PAVMs with feeding vessels 3 mm or larger greatly reduces the risk of embolic stroke. Complex PAVMs must have all feeding vessels embolized for success. Embolotherapy may reduce the risk of brain abscess, but abscess may recur even after successful therapy.[53] Although no data regarding efficacy exist, standard American Heart Association endocarditis guidelines for antibiotic prophylaxis before embolotherapy seem recommended. Because of the frequent observation of small persistent left-to-right shunt demonstrated by echocardiography even after successful embolotherapy, antibiotic prophylaxis is recommended for dental and other surgical procedures.

Serious complications of embolotherapy are rare. Because of the potential for systemic air and particulate embolism, all intravenous tubing is equipped with micropore filters and embolization precautions are taken. Air embolism during the procedure is rare, occurring in less than 5 percent in one series. It is generally manifested by perioral paresthesias or angina without permanent effect).[126] The most common postembolization symptom is pleurisy, and has been reported at rates ranging from 10-31%. [68, 73, 126] The onset may be delayed for up to 17 days in our experience, and severity may range from mild pain to a level of discomfort requiring hospitalization. These episodes are sometimes accompanied by large pleural effusions. The effusions and resulting hypoxemia always resolve within several weeks. Other complications have included migration of an embolic device, PAVM perforation, transient ischemic attack (TIA), early cerebral infarction after embolization. and paradoxical embolization of a device during deployment (4%). [48, 68, 90]

Diffuse PAVMs resulting in hypoxemia which are not amenable to embolotherapy represent a difficult problem. A few such cases have been successfully treated with lung transplantation. [102, 116]



Nester coil embolization



Amplatzer vascular plug

Cerebral AVMs – Treatment of cerebral AVMs remains a highly individualized decision. Important factors include size, location (silent or eloquent), symptoms, age, and patient preference. Treatment decisions generally involve experts in neurology, neurosurgery, neurointerventional radiology, and radiation oncology, as treatment options include resection with or without endovascular therapy, as well as gamma-knife radiotherapy.

Pulmonary hypertension – An uncommon complication, treatment is similar to that for primary pulmonary hypertension. A challenge for HHT is the tendency of epoprostenol infusion to increase bleeding. Bosentan has been reported to be useful,[133] and sildenafil may also be used.

Gastrointestinal bleeding – Most bleeding is due to GI telangiectasia. Patients with HHT may, of course, have bleeding for the same reasons as other members of the population. Rarely, variceal bleeding may occur due to transfusion-related hepatitis and cirrhosis, portal hypertension due to hepatic artery-portal vein AVMs, or liver fibrosis due to ischemia. Endoscopy is indicated on the first symptomatic occasion; however, multiple endoscopies are not indicated because local therapy is rarely successful, due to the diffuse nature of GI involvement. Improvement after systemic therapy with estrogen, antifibrinolytics, and somatastatin analogues is unpredictable. Anecdotal reports of improvement after systemic bevacizumab require confirmation.[151]

Liver disease – The most common manifestation of liver involvement is high-output heart failure due to left-to-right shunt. Heart failure therapy, emphasizing reduction of peripheral vascular resistance, may be useful as a temporizing measure. Optimal hemoglobin status may have a significant effect in

reducing high output; this may require surgical nasal therapy. Isolated case reports of improvement after systemic bevacizumab remain to be confirmed. The second most common presentation is with portal hypertension, which is accompanied by ascites and may result in variceal bleeding. Because liver function is normal, coagulopathy is absent and spontaneous bacterial peritonitis is rare. Hepatic artery embolization may result in short-term improvement, but may be accompanied by severe complications and is generally avoided at HHT treatment centers.[153, 154] Reports of improvement with bevacizumab require confirmation. [150, 152] Liver transplantation is the definitive treatment, and has excellent results,[155] though the total number reported is modest. A challenge for HHT center directors is achieving appropriate listing, as MELD scores are generally low compared to severity of illness.

PROGNOSIS

Mortality for all patients with HHT appears to be only slightly greater than for the general population. However, for patients identified at younger than 60 years of age, mortality rate was twice that expected. This is attributable to severity of disease[63], and is likely to be affected by ascertainment bias. Long-term population studies with genetically-based diagnosis are needed.

Educational materials for patients with HHT, and the location of specialized centers for managing HHT and PAVM are available from the HHT Foundation International at www.hht.org. Caregivers are also urged to consult the website for updated recommendations.

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