

## **CLINICAL MANIFESTATIONS OF HHT YALE OVERVIEW - 2004**

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Hereditary Hemorrhagic Telangiectasia (HHT) is a genetic disorder of blood vessels. Between 50,000 and 100,000 Americans are affected by HHT and most go undiagnosed. There are three types of HHT. Type 1 is caused by mutations in the endoglin gene and type 2 is caused by mutations in the ALK-1 gene, both of which encode proteins that are involved in the proper development of blood vessels. Recently, mutations in a third gene, SMAD4, have been found in families with both HHT and juvenile polyposis. Clinical genetic testing for HHT is available. HHT has variable expression in each affected member of a family. This is analogous to fingerprints, i.e. each patient has their own “fingerprint” (phenotype) despite having the same family mutation.

Mild to moderate nosebleeds are the most common symptom of HHT. The most common serious symptoms are ischemic stroke, TIA, and brain abscess, due to pulmonary arteriovenous malformation (PAVM) and hemorrhagic stroke and seizure due to cerebral arteriovenous malformation (CAVM). Gastrointestinal bleeding can also be problem in older adults with HHT. A smaller number of patients with HHT are affected by liver malformations, which can cause symptoms such as heart failure, abdominal pain and abnormal liver function tests (biliary type), or typical cirrhosis.

A common scenario in a family with undiagnosed HHT is the occurrence of a stroke or brain abscess that is treated without identifying the underlying cause of the problem. In these situations, when the PAVM/CAVM or its connection with HHT is not identified, the implications of the underlying disorder are not known to family members, and as a result affected relatives may also develop sudden catastrophic events instead of receiving counseling, screening, and treatment before complications occur.

About 10% of people with HHT die prematurely or are disabled due to complications of their vascular malformations. These “events” are preventable by early diagnosis, treatment and follow-up. Most patients are largely asymptomatic before their first serious complication.

Approximately 50% of patients with HHT have an AVM of the brain, lung, or liver, or a combination of 2 or 3 and will require therapy usually by a team of internists and interventional radiologists with expertise in this disorder. In North America, nine HHT centers have been developed over the past nine years at the University of Oregon, University of Utah, Washington

University St. Louis, University of California San Diego, University of Pennsylvania, the Mayo Clinic, Medical College of Georgia, University of Toronto, and Yale University. There are also centers in Europe, Asia and Australia ([www.hht.org](http://www.hht.org)). The following summary describes the diagnosis, management and follow-up of patients with HHT, as we currently recommend them at the Yale center.

## **DIAGNOSTIC CRITERIA**

The established clinical diagnostic criteria for HHT are:

- Nosebleeds (epistaxis), which are spontaneous and recurrent (may be mild or severe).
- Telangiectases on the skin or mucous membranes (mucocutaneous). Characteristic sites include the lips, oral cavity, fingers, and nose.
- Visceral arteriovenous malformations (AVMs), which may be located in the lungs, brain, liver, spinal cord, and GI tract.
- A first-degree relative with HHT, based on these diagnostic criteria.

A diagnosis of HHT is considered definite when three or more of these features are present, possible or suspected when two findings are present, and unlikely with fewer than two findings.

Clinical genetic testing for HHT is available through four labs in North America: University of Pennsylvania, ARUP University of Utah, HHT Solutions Toronto Canada, and Hospital for Sick Children.

## **PULMONARY ATERIOVENOUS MALFORMATIONS (PAVM)**

- PAVM are present in 30% of patients with HHT. They are a marker for HHT; 85-90% of people with PAVM have HHT. Diagnosis with a high sensitivity and specificity has been described recently, using contrast echocardiography (bubble study). Contrast echocardiography detects the presence of PAVM but does not determine size, location, or number of pulmonary malformations.
- When contrast echocardiography is positive, indicating a PAVM, thin section (5mm) chest CT without contrast material (UNENHANCED) is used to determine if treatment is necessary. PAVM with feeding arteries (i.e. the artery leading to the malformation) that are 3mm or greater in diameter, should be treated. Individuals with PAVM of this size or larger are at risk for stroke or TIA due to passage of small clots through the malformation. The potential for brain abscess is reduced by treating all 3 mm diameter arteries leading to PAVM, but NOT eliminated, hence the need for continued antibiotic prophylaxis before dental work and invasive procedures.
- Treatment of PAVM consists of transcatheter embolization, a non-surgical procedure done under local anesthesia in adults and general anesthesia in children. The procedure is performed by interventional radiologists who are specially trained and qualified in non-surgical image guided therapies. Fibered platinum coils and in some instances balloons are placed in the artery to the PAVM to occlude them internally, achieving the same result that thoracic surgeons did by tying off the artery or removing lung, but avoiding the chest incision and the post operative complications.
- Follow-up of patients with treated PAVM is CRITICAL. By six months after treatment, the PAVM should be gone, leaving a residual scar, or should be markedly reduced in size. This should be confirmed by chest CT WITHOUT contrast. If the

AVM is still present, which occurs in 5-10% of patients, it should be retreated. Once treated PAVM are shown to be gone, the patient should be followed with unenhanced chest CT every 5 years in order to assess growth of any small AVM, until the threshold size (3mm diameter feeding artery) is reached.

- Antibiotics are required before dental work and bacteremic procedures in individuals with PAVM for the rest of their lives.
- In patients with HHT who DO NOT have PAVM, we currently believe that additional lung screening is not required, nor are prophylactic antibiotics before dental visits. However, we recommend that patients stay in touch with the HHT Foundation/HHT center and visit an HHT center every 5 years, as recommendations change.

### **CEREBRAL ARTERIOVENOUS MALFORMATIONS (CAVM)**

- CAVM are present in 10-20% of patients with HHT and are often multiple. They are not a marker of HHT as only approximately 10% of patients with CAVM have HHT. Unlike PAVM, CAVM, occur fairly commonly in people without HHT.
- 10-12% of individuals with HHT have a CAVM that is 10mm in diameter or greater.
- Treatment by embolization, stereotactic radiosurgery, or neurosurgical removal, should be considered in those with CAVM that are 10mm or greater in diameter. At present, the precise indications and timing of treatment as well as screening protocols are not established.
- Patients with treated cerebral AVM need a follow-up angiogram at one year to prove that the CAVM is gone and follow-up MRI to detect growth of other CAVM.

### **EPISTAXIS (NOSEBLEEDS)**

- 90% of people with HHT have nosebleeds ranging from mild to severe.
- Transfusion dependent nosebleeds occur in about 20% of people with HHT.
- Skin grafts, hormonal therapy, other medical therapy, or a combination of these treatments can be helpful in these patients.
- Embolization of the blood vessels in the nose is helpful in emergent situations but is not durable for more than 4-6 weeks.
- Laser therapy can be helpful in individuals with moderate nosebleeds.
- The best therapy to date in those who are transfusion dependant is the application of skin grafts by the technique developed by Dr. William Saunders, of Ohio State University, which is referred to as the Saunder's method.
- Hormonal and antifibrinolytic therapies are useful, but potentially dangerous in patients with untreated or partially treated PAVM.

### **LIVER ARTERIOVENOUS MALFORMATIONS**

- Symptomatic liver malformations occur in less than 5% of people with HHT.
- Asymptomatic liver malformations are present in up to 70% of people with HHT.
- Patients with symptomatic liver AVM may present with three distinct clinical syndromes: high output heart failure, biliary obstruction (abdominal pain and abnormal liver functions tests), or cirrhosis.
- The natural history, treatment, and indications for liver transplant or other therapies are not understood at this time.

- Liver artery embolization is risky and leads to mortality in 20% of patients.
- Liver biopsy and ERCP can be harmful. Advice from an HHT center should be obtained if these procedures are being considered.

## **GASTROINTESTINAL BLEEDING**

- Gastrointestinal bleeding occurs in 20% of people with HHT, usually in the 6<sup>th</sup> and 7<sup>th</sup> decades of life.
- Gastrointestinal bleeding usually arises from telangiectases (small AVM) in the stomach, duodenum, and small bowel.
- Laser and bicap techniques have not been shown to be helpful long term.
- Therapies including hormonal and antifibrinolytic medications are useful, but doses and duration of treatment are not certain at this time. Using this type of therapy is also potentially dangerous in patients with untreated or partially treated PAVM. Hence the importance of establishing the complete “fingerprint” (phenotype) of patients with HHT.

## **SUMMARY**

HHT is a genetic disorder associated with small AVM (telangiectases) of the skin, nose, and GI tract, and larger AVM of the brain, lung or liver. The AVM in the lung and brain are treatable but because AVM can continue to grow/enlarge, patients need careful and continued monitoring. Once an individual with PAVM and most probably HHT is identified, the family should receive genetic counseling and screening.

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