

## **YALE HHT CENTER ACCOMPLISHMENTS: 1995- 2008**

### **CLINICAL RESEARCH SUMMARY**

During the first years of operation of the Yale HHT Center, the focus of our clinical research was the evaluation of current treatments and the development of new therapies for pulmonary arteriovenous malformations (PAVM), nosebleeds (epistaxis), gastrointestinal bleeding, cerebral arteriovenous malformations (CAVM), and liver involvement by HHT. An overriding concern expressed by you and your families was the care of children. Below is a summary of what we have learned from our research during these past 11 years.

#### **Pulmonary Arteriovenous Malformations (PAVM) (References 1-14)**

We have developed new coil techniques to replace the detachable balloon method for treating PAVM and we have shown that the coil techniques are equally efficacious to the balloon techniques.

Equally important is the long-term outcome of patients treated during the 1996-99 timeframe. Specifically, we have shown that regular follow-up after treatment is important (the PAVM should disappear) and that occluding all PAVM of a certain size protects the patient against stroke and hemorrhage.

Finally, we have demonstrated that treating PAVM in children is necessary when they are large to prevent lung hemorrhage. Our latest paper, published in 2006, demonstrated that embolotherapy was curative of most focal PAVM and protective against stroke and pulmonary hemorrhage in children and adults. A paper in press due to appear in 2008, describes our experience with a diffuse form of PAVM which occurs in children and adults. We have also developed an exercise test in conjunction with the pediatric cardiology exercise laboratory at Yale which we feel will replace some of the imaging we do to evaluate and follow our patients.

Patients need continued antibiotic prophylaxis 1 hour before dental cleaning and they should return to the HHT Center for update evaluation at least every 5 years.

#### **Nosebleeds (Epistaxis) (References 15-18)**

In conjunction with Dr. Douglas Ross, we have shown that his modification of the Saunders dermoplasty, the skin grafting procedure used to treat severe nosebleeds, is able to stop transfusion dependent epistaxis in 90% of patients. We have confirmed that embolization of nasal arteries provides only temporizing results and should not be done as a palliative measure. Dr. Ross has demonstrated that once a year focal laser therapy done specifically when the patient is not bleeding and in a manner that preserves the mucosa is very effective for palliation and relief of nosebleeds that interfere with quality of life.

To further evaluate management of mild nosebleeds and in particular trials of natural methods which patients can apply at home, multicenter trials will be necessary. We have shown that the Ross Severity index (below), works well in evaluating nosebleeds in over 2500 patients. This index needs testing in multiple centers but for now remains an important guideline for evaluation and management of epistaxis in our patients.

**YALE EPISTAXIS SEVERITY INDEX**

SEVERITY	FUNCTIONALITY	ANEMIA	RX FOR ANEMIA	SUGGESTED TREATMENT
Mild	Unaltered	No	N/A	Supportive care
Moderate	Altered	Yes	Oral Iron*	Laser
Severe	Crippled	Yes	Repeated transfusions (blood and Fe)**	Septal Dermoplasty

\* Patients in the moderate category may have had 1 infusion of blood or iron since so many come to us severely iron depleted

\*\* Patients in the severe category have continued need for blood transfusions and IV iron infusions.

**Gastrointestinal Bleeding (References 19-21)**

In conjunction with Dr. Deborah Proctor, we have reported the largest group of patients with gastrointestinal bleeding associated with HHT. In 50% of these patients we were able to stop gastrointestinal bleeding using medications. Further, we have demonstrated that telangiectases occur frequently in the small intestine as well as stomach and duodenum. This has importance since cauterization cannot be done in the small intestine and provides the basis for us to go forward to look for new medications to control bleeding.

Drs. Proctor and Ross have demonstrated that if we can control nosebleeds and provide adequate iron replacement to patients requiring transfusions, this may be enough to maintain their hemoglobin. If oozing telangiectases are present in the stomach and small bowel, we judiciously treat patients with certain medicines, if blood transfusions are still required.

We have also shown that patients requiring medicines for control of bleeding should be evaluated first for the status of their pulmonary malformations. Some medicines will cause blood clotting which can lead to passage of clots through the PAVM and neurological problems. Thus patients should be evaluated before starting medicines to promote clotting. Similarly, patients with other illnesses can receive anticoagulants if they are evaluated first in their HHT Center and if necessary undergo nasal treatment by an HHT doctor with expertise in management of nosebleeds.

**Hepatic (Liver) Arteriovenous Malformations (References 22-30)**

In conjunction with Dr. Guadalupe Garcia-Tsao and Dr. Lawrence Young, we have defined 3 types of clinical involvement of the liver by HHT. Further, we have demonstrated that embolization of the liver is dangerous as a treatment for HHT liver disease. We have shown that serious liver involvement occurs in about 5% of patients with HHT.

Drs. Young and Garcia have pioneered an important medical approach to symptomatic patients with heart failure due to liver malformations. We are hopeful that as funding becomes available, multicenter trials using their techniques will prove equally efficacious in other centers and also delay the need for more invasive therapies

**Brain Involvement (References 31-35)**

We have proven that PAVM with arteries 3 mm in diameter and larger are associated with paradoxical emboli and are the ones that must be treated. We have also proven that brain arteriovenous malformations occur in about 10% of patients with HHT. Once the patient has a normal brain MRI, there is no need for further screening.

There has been some debate about the need for brain MRI in patients with HHT. We have found it extremely helpful in managing patients to have a baseline MRI for all patients. In addition to screening for brain AVM, many of our patients with PAVM have abnormalities which are not primary brain malformations but are secondary to migraines or small paradoxical emboli through untreated PAVM.

## **THE FUTURE**

We predict a number of projects will be initiated to identify new medications for controlling gastrointestinal bleeding which occurs in about 10% of patients with HHT. Now that we have shown that local therapy with endoscopic control (e.g. laser, cautery) is not efficacious in many patients, this should provide the stimulus for the development of new drugs to control of bleeding.

Over the next 5 years, improvements in the management of patients with liver malformations will occur including recognition by the transplant community that liver transplant is effective therapy for the 2.5% of HHT patients with severe involvement.

We are in the process of defining the algorithms for screening and treatment of children with PAVM and cerebral arteriovenous malformations.

Most importantly, we have shown in a large center that there is a need for careful coordination between the physician director working with the genetic counselor and the many subspecialists caring for a patient with HHT.

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