

Summary of the 8th International HHT Conference

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The 8th International HHT Conference was held May 27-31, 2009 in Santander Spain. The view was breathtaking from the venue which was on a peninsula jutting into the Mediterranean sea. However, the science was even more breathtaking for the 250 participants. There were so many excellent presentations that it would be impossible to discuss them all. Therefore, I will discuss some of the research that I personally found most interesting with apologies to those (the majority) that I have not included in this brief summary.

As always, there were many interesting presentations on the genetic diagnosis of HHT and differences in the clinical features between patients with different genetic types (e.g. ALK1 versus endoglin). Presentations at prior conferences suggested that mutations on chromosome 5 and 7 may also be causes of HHT. A US group provided further support for an HHT gene on chromosome 7 and ongoing work is trying to narrow down the exact gene. Another US study interviewed 20 patients about their experience with genetic testing and found that most had a good understanding of the results and encouraged other family members to have genetic testing themselves in order to obtain a more speedy and accurate diagnosis. Unfortunately, relatives often declined testing due to a variety of reasons such as fear of losing insurance or fear of being diagnosed. Recent passage of the Genetic Information Nondiscrimination Act (GINA) and advances in treatment make these concerns less valid and highlight the need for patient and provider education. Many studies have previously shown that patients with HHT1 (endoglin mutation) are much more likely to have pulmonary AVM than patients with HHT2 (ALK1 mutation). 3 groups (France, Netherlands, and US) further showed that HHT1 was associated with more numerous pulmonary arteriovenous malformations (AVM), especially small ones, and a much greater degree of shunting of blood flow through the AVM.

It has long been suspected that the vascular malformations seen in HHT are due to the combination of a genetic mutation plus some type of second hit. Support for this theory was given by 4 groups (1 UK and 3 USA) using various mouse models and even a zebrafish model. In these models, blood flow, tissue injury, and repetitive pressure on skin were found to be important determinants of abnormal vascular development in animals with either ALK1 or endoglin deficiency. Findings such as these will make it easier to study the causes of the vascular changes and to test potential treatments.

HHT is typically seen as a disorder due to defective cells that line the blood vessels. Several groups showed data to suggest that HHT may also involve proteins that travel in the blood. A Netherlands group showed that circulating blood cells had a defective ability to respond to injured heart cells. A Spain group found that the concentration of several proteins was reduced in the blood of HHT patients, suggesting they may be useful as a diagnostic test. These findings support the concept that some of the problems in HHT may be due to more than just defective cells that line the blood vessels.

There were numerous presentations exploring the role of various proteins and receptors in causing the effects of HHT. One of the most interesting was presented by a France group who showed that the blood protein BMP9 normally attaches to ALK1 and acts to stabilize or suppress the formation of new blood vessels. However, in HHT patients, this mechanism is defective and results in an activated state of blood vessel formation (so-called angiogenesis). This suggests that therapies directed against blood vessel formation may be beneficial in HHT.

A Netherlands group reported on a study of over 900 patients that compared the validity of the Curacao diagnostic criteria compared with genetic testing, and showed that they were still valid. They also showed that the number of telangiectasia increased with age, even in patients without HHT, suggesting that the threshold for using telangiectasia should be age dependent. A cooperative Canada and Netherlands study also showed that the life expectancy of patients with HHT was about 70 years for men and women; this was no different for men without HHT, but was a little lower than women without HHT. Canada and UK groups showed that the vast majority of pregnant women with HHT had successful pregnancies, especially if they were diagnosed and under care for their HHT, and were screened for pulmonary AVM before pregnancy. HHT Centers have generally advocated to avoid the use of blood thinners due to an increased risk of bleeding. A US group reviewed their experience with the use of blood thinners such as warfarin for patients with blood clots and found that it could be used safely in selected patients

There were over 20 presentations related to pulmonary AVM (PAVM). A Canada group showed that in patients who had positive shunt on a bubble echo AND a normal chest CT (i.e. the PAVM were likely too small to be detected by CT), the risk of complications from PAVM was very low. Two groups (UK and USA) looked at the risk of embolizing PAVM in patients with underlying pulmonary hypertension. Although it can be done safely in many cases, several patients have had serious complications; it remains difficult to predict who will do well and who will have problems. 4 groups (Netherlands, Norway, UK, and USA) presented data showing that use of the new Amplatzer vascular plugs were highly effective in occluding PAVM and had a low incidence of recanalization in follow up. Three groups (France, Italy, and Netherlands) confirmed that bubble echo was very sensitive in detecting PAVM that were large enough to require treatment and quite safe. In the last several years, several national organizations in the US and UK have narrowed their recommendations for the use of antibiotic prophylaxis prior to various procedures. A UK group reviewed these recommendations and concluded that antibiotic prophylaxis should still be recommended for HHT patients with PAVM prior to dental and surgical procedures.

There were several exciting talks on the use of anti-angiogenic drugs (drugs that can decrease the formation of blood vessels) to treat various complications of HHT. Thalidomide and bevacizumab are two such anti-angiogenic drugs. Telangiectasias and AVM are due to the abnormal growth of blood vessels in HHT. Bleeding - mainly from the nose and intestines - remains a serious problem for many patients with HHT. Most can be controlled with various treatments, but about 5-10% are dependent on blood transfusions. Two groups (Italy and US) showed preliminary data suggesting that oral thalidomide can decrease the need for blood transfusions in patients with nosebleeds and/ or intestinal bleeds. A France group is starting a study to look at the use of bevacizumab to treat patients with heart failure due to liver AVM. Liver transplant is another treatment that has been used for severe liver AVM. A France group showed that amongst 13 patients who underwent liver transplantation for liver AVM, 12 were still alive 7 years later and most experienced an improvement in their quality of life.

A US group presented the results of a study funded by the HHT Foundation to develop a method for categorizing epistaxis severity. 914 patients filled out an online survey that included 120 questions about the severity of their nosebleeds. These data were then used to develop a scoring system based on answering 6 simple questions about one's nosebleeds. This is the first statistically studied epistaxis severity index and will hopefully be useful in conducting clinical research and treating patients with HHT. An Israel group presented one of the few randomized

controlled trials of a medication for nosebleeds. In a study of 25 patients, oral tamoxifen was found to improve the frequency and severity of nosebleeds compared with placebo. Two groups (German and US) showed that Young's procedure - surgical closure of the nostrils - was highly effective in stopping nosebleeds in selected patients. This radical sounding procedure was 100% effective in controlling nosebleeds, was associated with only mild to moderated side effects, and improved the quality of life of these HHT patients.