Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia (HHT), also called Rendu-Osler-Weber syndrome, is inherited as an autosomal dominant trait. HHT was first described in 1864 by Sutton and further reviewed by Osler, Weber, and Rendu and named by Hanes.\(^1\) The prevalence is estimated at 1 in 10,000.\(^2\)

Characteristics of the disease include a family history of hemorrhage and the presence of flat, red, or purple lesions (telangiectasias) on mucous membranes. The lesions occur on the lips, the tongue, and entire gastrointestinal tract, on the respiratory tract, and on the palms and soles of the feet. At autopsy, they can be found in any organ. The spots may be up to 3 mm in diameter and sometimes coalesce to become layered and spider-like. They blanch with pressure.

The telangiectasias are composed of unusual dilated blood vessels in which arterioles are directly connected to venules because the capillaries that should be between them have disappeared. The walls of the vessels are thin and fragile, and the endothelial cell junctions are also defective, leading to rupture and bleeding.

In most patients, the cause of HHT is mutations of a gene on chromosome 9q for a glycoprotein called endoglin. Endoglin is a receptor for transforming growth factor-\(\beta\) on the surface of endothelial cells. Mutations of two other genes have been identified in some families, one of which is on chromosome 12 and also is related to the receptor for a different type of transforming growth factor-\(\beta\). The role that the transforming growth factor receptors play in forming the lesions is not known.\(^2\)

The telangiectasias begin to develop in childhood and become more numerous with age. Symptoms may begin in childhood or in early adult life to middle age. Epistaxis is the most common manifestation. Slow progressive bleeding from lesions in the gastrointestinal tract can lead to a hypochromic anemia. Up to one-half of patients have multiple lesions in the lungs that cause decreased oxygenation of blood and may result in thrombosis.\(^3\) In the homozygous state the disease is fatal.

Laboratory screening tests are normal. The only treatment for hereditary telangiectasia is supportive and symptomatic care.

Additional web sites that may be of interest:
http://www.familyvillage.wisc.edu/lib_ht.htm
http://www.mc.vanderbilt.edu/peds/pidl/genetic/oslerweb.htm
**Ehlers-Danlos Syndromes**

The Ehlers-Danlos syndromes are a group of disorders in which there is abnormal and decreased synthesis of subendothelial collagen. Synthesis of collagen is very complex. Twenty genes are known to code for the primary amino acid sequences, and several enzymes are involved in post-translational modification of the proteins. From these, at least 10 distinct types of collagen are produced. An abnormality in any one gene can result in decreased synthesis of one of the collagen types or in the production of one type of collagen with a variant amino acid sequence. The result is the phenotype recognized as Ehlers-Danlos syndrome. At least 11 syndromes are included in the Ehlers-Danlos group based on clinical characteristics and inheritance pattern.

Most of the Ehlers-Danlos syndromes are inherited with an autosomal dominant pattern. Ehlers-Danlos syndrome, Type IV, is caused by mutations in a gene on chromosome 2 for type III collagen called COL3A1. Type III collagen is a major component of arterial walls, the bowel wall, and the uterus.

Clinical characteristics of Ehlers-Danlos syndromes vary from patient to patient. Bleeding manifestations occur because extreme fragility of the vessels allows blood to leave the lumen and enter the tissues. Easy bruising, spontaneous bruising, petechiae, and gastrointestinal, gingival, and dental bleeding are common. Arteries, the intestine, or the uterus may rupture spontaneously. Other clinical features include extraordinary stretchability of the skin; fragility of the skin, producing large wounds with trauma; difficulty in surgical closures of wounds; and hyperextensible joints.

Laboratory tests for hemostasis are usually normal, although the bleeding time may be abnormal. Therapy is supportive.

Additional web sites that may be of interest:

- [http://www.orthop.washington.edu/arthritis/types/ehlersdanlos/01](http://www.orthop.washington.edu/arthritis/types/ehlersdanlos/01)
- [http://www.mc.vanderbilt.edu/peds/pidl/genetic/ehlers.htm](http://www.mc.vanderbilt.edu/peds/pidl/genetic/ehlers.htm)

**Marfan’s Syndrome**

Marfan’s syndrome demonstrates autosomal dominant inheritance and is also the result of spontaneous mutations in one-fourth of all patients. It is caused by mutations in the gene for fibrillin-1 on chromosome 15. Fibrillin is a component of connective tissue that gives strength and elasticity to blood vessels.

Characteristic defects are long extremities, spidery fingers, dislocation of the lens, and hyperextensible joints. The aorta is prone to aneurysms (dissecting and ascending) because the wall is weaker. Athletes with Marfan’s syndrome have suffered instant deaths because of rupture of the aorta. A defect of the mitral valve of the heart is the most common cause of death. Easy bruising may occur. Laboratory features may include a prolonged template bleeding time and variable abnormalities of platelet aggregation, but they are not specific.
**Osteogenesis Imperfecta**

Osteogenesis imperfecta also is transmitted in an autosomal dominant manner. It is a group of disorders of the genes for type I procollagens that cause a patchy, defective bone matrix. The result is extremely brittle bones that fracture easily. The phenotype ranges from the probability of death in utero or at birth because of collapse of the cranial bones to fractures with trauma only. Bleeding symptoms include intracranial hemorrhage, easy and spontaneous bruising, epistaxis, and hemoptysis. Laboratory tests nonspecifically may show an abnormal template bleeding time and abnormal platelet aggregation studies.

**Pseudoxanthoma Elasticum**

This rare group of disorders, inherited in an autosomal recessive manner, is the result of calcified elastic tissue in the skin and all arteries. The molecular basis is as yet unclear. Symptoms may not appear until the second or third decade of life and then may involve hemorrhage in any organ because the vessels rupture. The gastrointestinal tract, eyes, kidney, nose, and skin are particularly prone to hemorrhage. Easy bruising, petechiae, and purpura are commonly found. Some patients may have a tendency to develop thrombosis and acute myocardial infarction. The template bleeding time may be prolonged.

**REFERENCES**


