Buerger's Disease, History, Diagnosis, Treatment

FREE STUDY AT THE CHOLESTEROL CENTER, JEWISH HOSPITAL, CINCINNATI OH
(PHONE 513-924-8250, FAX 513-924-8273, EMAIL glueckch@healthall.com)

If you have well defined Buerger's disease, we may be able to help devise a safe, case-specific medical intervention, depending on the presence or absence of two gene polymorphisms associated with arterial spasm, and a mutation associated with abnormalities in homocysteine metabolism. You can call the Cholesterol Center (513-924-8250) to make an appointment for this entire free study, which will take about 1.5 hours of your time and a small blood sample. Alternatively, if you cannot get to Cincinnati, we can work with you through the MDL laboratory of Cincinnati (513-475-6631). Have your physician draw a 5 cc purple top tube of blood so that the crucial PCR tests can be done and mail it unrefrigerated in a crush-proof container, overnight or 2-day delivery to MDL, 3130 Highland Ave. Cincinnati, OH 45219.

Read more about Buerger's disease and our promising new studies below.

HISTORY:  top

Buerger's disease (BD) (also known as thromboangiitis obliterans) is a rare disorder (incidence 1/8000 people), which is much more common in men than in women, and is closely associated with heavy cigarette and/or cannabis smoking, or rarely, with tobacco chewing. Buerger's disease appears to be more common in Asians and in the Middle East, is rare among African-Americans, and is very rare in children. Buerger's disease is characterized by severe spasm of peripheral arteries and arterioles, usually in the feet and lower legs, but sometimes in the arms and hands. At the same time, commonly, there is extensive blood clotting of arteries and arterioles in the hands and feet. Oxygenated blood cannot then get to the tissues; peripheral skin ulcers and gangrene then develop, along with intractable pain.

In 1879, Felix von Winiwater (1829-1894) dissected and studied in detail the amputated right leg of a 57-year old man suffering from 'spontaneous gangrene'. Histologic examination demonstrated extensive small arterial and venous occlusions marked by hypercellular thrombus and preservation of the internal elastic lamina. Leo Buerger (1879-1943), working at Mount Sinai Hospital in New York, reported the results of pathologic examination of 11 amputated limbs from young men in whom progressive veno-occlusive disease resulted in amputations. Buerger termed the entity 'Thromboangiitis Obliterans'.

BD is seen primarily in smokers. There is a male to female predominance of 9:1. Early in the disease patients present with isolated episodes of superficial phlebitis and episodes of foot and leg pain. This progresses rapidly to skin ulcers and gangrene. BD primarily involves the lower extremities. Involvement of the only the upper extremity is seen in 40% of patients. BD should be suspected in a young smoker with symptoms indicative of peripheral vascular disease, with no risk factors for atherosclerosis or thrombotic disease.

Currently, the initiating factor in BD is not known. The hypothesis is that a tobacco-related antigen initiates the pathology. BD is seen in pipe, cigarette, and cannabis smokers, and rarely in subjects chewing tobacco. There is a strong association between smoking and disease progression. Improvement in symptoms is dependent on cessation of smoking. In BD, there is an association with HLA-A9, HLA-B5, and the combination HLA-B54 and MICA 1.4. HLA-B 12 is considered protective. Cell mediated and antibody responses to collagen type I and III, major constituents of the arteries have been demonstrated along with antibodies to elastin. There is consumption of CH50 and reduced levels of C3. To date, studies exploring the causes of BD have included few patients and remain inconclusive. The etiologic factors in BD remain elusive. The acute pathological lesion in BD is characterized by total arterial luminal obliteration with a cellular thrombus containing micro abscesses of polymorphonuclear cells surrounded by mononuclear epithelioid cells. This is no suggestion of vessel wall necrosis. There is preservation of the internal elastic lamina (IEL) with deposition of IgG, IgM, IgA, C3d and C4c on the inner aspect of the IEL. Foam cells, cholesterol clefts, fibrous intimal proliferation, hyaline degeneration and calcifications, commonly seen atherosclerosis, are not present. MTHFR C677T homozygosity or C677T/A1298C compound heterozygosity are associated with decreased activity of MTHFR leading to low levels of plasma folate and hyperhomocysteinemia. MTHFR is located on chromosome 1(1p36.3); it is involved in methionine metabolism and single-carbon transfer pathways. The population prevalence of MTHFR C677T homozygosity is estimated to be 12% and the prevalence of MTHFR C677T/A1298C compound heterozygosity is estimated to be 17%. Hyperhomocysteinemia is atherogenic and thrombogenic, and is associated with an increased incidence of arterial and venous occlusive disease. Hyperhomocysteinemia converts endothelium to a more
prothrombotic state by increasing Factor V, XII, and Tissue Factor; inhibiting thrombomodulin expression; and decreasing Protein C activation. Homocysteine, when added to plasma, is readily oxidized. During oxidation, superoxide anion radical and hydrogen peroxide are generated. These are believed to account for endothelial cytotoxicity in hyperhomocysteinemia. Nitric Oxide (NO), Endothelium-Derived-Relaxing-Factor, is a vasodilator and paracrine molecule with pleiotropic effects including inhibition of platelet aggregation. Endothelial dysfunction is associated with impaired NO production. Endothelial Nitric Oxide Synthase (eNOS), using L-arginine as the substrate, produces NO. Superoxide anion radicals produced in the presence of hyperhomocysteinemia react with Nitric Oxide (NO), resulting in the formation of peroxynitrite and less bioavailability of NO. Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of eNOS, is derived from hydrolysis of protein containing methylated arginine. Elevated ADMA levels are present in hyperhomocysteinemia.

L-arginine enhances NO synthesis, improves endothelial dilatation, decreases platelet aggregation, and reverses endothelial dysfunction. Oral supplementation with folate reduces plasma homocysteine levels in the presence of isoenzymes of MTHFR with reduced enzymatic activity.

**SYMPTOMS-PHYSICAL FINDINGS:**

The most characteristic features of Buerger’s disease include the following:

- Unexplained and commonly intractable pain, tenderness, or numbness-tingling in the limbs accompanied by skin ulcers or gangrene of the fingers or toes.
- Symptoms worse with exposure to cold and exercise.
- Reduced or absent peripheral arterial pulses

**DIAGNOSIS:**

The definitive diagnostic methods include an arteriogram of the affected extremities with a concomitant Doppler ultrasound

**THERAPY:**

Currently, the only known therapies for Buerger’s disease are immediate cessation of smoking and supportive treatment for the skin ulcers and gangrene; amputation is occasionally required.

**NEW DIAGNOSTIC AND THERAPEUTIC INFORMATION:**

Recent studies at the Cholesterol Center of the Jewish Hospital of Cincinnati and MDL laboratories in Buerger’s disease have implicated two apparently pathoetiologic genetic polymorphisms (stromelysin-1 5A/6A, eNOS T-786C) and one gene mutation (MTHFR C677T-A1298C). The stromelysin-1 5A/6A and eNOS T-786C polymorphisms are associated with arterial spasm and reduced production of the body’s major vasodilator, nitric oxide (NO). The MTHFR mutation is thrombogenic and may interfere with NO production. Documentation of these gene polymorphisms and MTHFR mutations open new, successful, therapeutic avenues which include 15g/day of L arginine orally (to increase NO production and decrease vasospasm), and folic acid (5 mg), vitamin B6 (100 mg), and vitamin B12 (2000 mcg) to normalize homocysteine metabolism.

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