

REVIEW

Thrombophilia and Other Conditions Associated With Acute Cardiovascular Syndromes

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ABSTRACT

Although the classical risk factors are found in the majority of patients with acute coronary syndromes, in a good percentage, particularly young patients, known modifiable risk factors are not present. In this subgroup of patients with acute coronary events, thrombophilia or hypercoagulable states have been suspected and several genetic variants (polymorphisms) have been found in genes related to coagulation proteins, fibrinolytic system, platelet receptors, homocysteine metabolism, platelet receptors, endothelial dysfunction, and abnormal blood flow. Angioproliferative disorders have also been reported as associated with non-atherosclerotic coronary disease. In this brief overview, such nonclassical risk factors and causes of coronary events are discussed.

KEY WORDS: *electrode catheters, pacemakers, device reuse, re-sterilization process, device infection*

INTRODUCTION

Currently the established risk factors for cardiovascular disease are largely related to atherosclerosis or better termed atherothrombosis. Coronary artery thrombosis is the critical event precipitated by a ruptured atherosclerotic plaque leading to acute coronary syndromes (myocardial infarction and unstable angina). The existence of a prolonged hypercoagulable state preceding the thrombotic event has been postulated for some time and a significant association has been established between the plasma concentrations of a number of hemostatic variables and the frequency of myocardial infarction.¹⁻¹⁴ High plasma fibrinogen, factor VII/VIIa, tissue-type plasminogen activator and plasminogen activator inhibitor levels have been associated with at least as great a risk of developing myocardial infarction as cholesterol levels, especially in the young.

In recent years more sensitive tests have been developed which could allow for a more precise biochemical definition of hypercoagulable states.^{3,6,8,10,13,14} Mutations in specific coagulation genes may also provide a genetic basis for cardiovascular disease risk.⁹ The impact of certain genotypes must be examined in relation to other established risk factors and potentially new therapeutic strategies.

ABBREVIATIONS

ALHE = angiolymphoid hyperplasia with eosinophilia

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GENETIC RISK FACTORS IN ACUTE CORONARY DISEASE

Among others, mutations or polymorphisms of HPA-1, factor V Leiden, prothrombin gene variant and the methylene tetrahydrofolate reductase gene (MTHFR) are now listed as novel risk factors for acute coronary artery disease.^{4,8,9} Until recently laboratory diagnosis of thrombophilia was based on investigation of the plasma anticoagulant pathways to detect antithrombin, protein C, and protein S deficiencies and on the search of dysfibrinogenemia and anti-phospholipid antibodies/lupus anticoagulants. More recently, laboratory investigations have been expanded to include activated protein C (APC) resistance, attributable or not to the presence of the factor V Leiden mutation, hyperthrombinemia attributable to the presence of the prothrombin gene mutation G20210A and hyperhomocysteinemia attributable to impairment of the relevant metabolic pathway because of enzymatic and/or vitamin deficiencies.^{1-3,6,8-10,13,14} Education and patients' compliance are essential to successful long-term management of these conditions.

MYOCARDIAL INFARCTION IN PATIENTS WITH NORMAL CORONARY ARTERIES

Up to 50% of patients with coronary artery disease may not have any of the conventional risk factors. Generally there is an inflammatory and a vasomotor component in the pathophysiology of the acute coronary event in patients with normal coronary arteries. *Prinzmetal's variant angina, syndrome X, coronary embolization* and *congenital coronary anomalies* are a few examples of conditions that may not be associated with coronary atherosclerosis and established risk factors. Novel risk factors that are emerging in an attempt to establish an etiology in this group of patients are plasma *homocysteine*, plasma fibrinogen, estrogen-deficiency, lipoprotein(a), C-reactive protein, chlamydia pneumoniae, helicobacter pylori, factor VII, endogenous tissue plasminogen and endogenous plasminogen activator/inhibitor type I.^{1,2,5-10,13,14}

An elevated level of total *homocysteine* in blood is emerging as a prevalent and strong risk factor for atherosclerotic vascular disease in the coronary, cerebral, and peripheral vessels and for arterial and venous thromboembolism.^{1,2} Hyperhomocysteinemia arising from impaired methionine metabolism probably usually due to a deficiency of cystathionine beta-synthase is associated with premature cerebral, peripheral and possibly coronary vascular disease. However, it is not entirely clear whether hyperhomocysteinemia is a risk factor or a consequence of ischemic heart disease, and its role in patients with premature coronary artery disease is

not certain. Although there is a considerable epidemiologic evidence for a relationship between plasma homocysteine levels and cardiovascular disease, not all studies have shown such a relationship. Nevertheless, latest studies show that hyperhomocysteinemia represents an independent risk factor for acute coronary thrombosis rather than for the development of coronary atherosclerosis. Therefore, hyperhomocysteinemia may influence the clinical situation after plaque rupture not only by prothrombotic action but also by favoring endothelial dysfunction and vasospasm.

ANGIOPROLIFERATIVE DISORDERS AND ISCHEMIC HEART DISEASE

Kimura's disease is an allergic, inflammatory disorder of unknown cause. It mainly affects men who present with lymphadenopathy, peripheral eosinophilia and elevated serum IgE.^{11,12} *Angiolymphoid hyperplasia with eosinophilia (ALHE)* is another angioproliferative disorder. Endothelial proliferation is more pronounced in Kimura's disease and is lacking the atypical histocytoid endothelial cells characteristic of ALHE. Compared with Kimura's disease, ALHE is more variable in its clinical, histopathologic and immunohistochemical features. Subcutaneous mass lesions of the head and neck are common in angiolymphoid hyperplasia with eosinophilia as well as in Kimura's disease, most often in the periauricular location in young and middle-aged adults. In ALHE the lesions are smaller and more superficial. The diagnosis is confirmed by biopsy. Various treatment modalities have been suggested for the management of these conditions. Oral corticosteroids have been the mainstay of therapy.

In the literature there are a few cases of young patients with hyper eosinophilia associated with Kimura's disease who showed repeated life-threatening syncopal attacks during daily activities or at rest or presented with acute myocardial infarction. Coronary angiograms demonstrated small aneurysms with irregular vessel walls of coronary arteries and the absence of organic stenotic lesions. These case reports suggest the need to extend the concept of conventional risk factors for coronary artery disease in young patients with myocardial infarction and normal coronary arteries.

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