Inherited Hypercoagulable Disorders in the Elderly

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Old age is considered a significant risk factor for venous thromboembolism (VTE), and the incidence of VTE increases exponentially with age. Associated comorbid conditions such as heart failure, postoperative states, malignancy and long-term immobility contribute considerably towards the higher incidence of these hypercoagulable disorders in this subgroup of patients. The optimal, cost-effective laboratory work-up for underlying thrombophilic or hypercoagulable states is not clear in older patients. The main aim of this article is to review the inherited thrombophilic disorders and discuss their clinical relevance in older patients.

Key words: hypercoagulable disorders, thrombophilia, venous thromboembolism, risk factors.

Introduction

Hypercoagulable states, or thrombophilic, are defined as a propensity to develop spontaneous venous or arterial thrombosis in association with various inherited or acquired disorders. Although these disorders put an individual at higher risk for thrombosis, they do not actually cause thrombosis by themselves. Over the last decade, scientific advances in the field of thrombosis have made a significant impact on the management of thrombotic disorders. The main influence of these advances has been on the diagnosis and screening strategies of underlying inherited thrombophilic disorders, especially in young patients.

Old age is considered to be a significant risk factor for venous thromboembolism (VTE), and the incidence of VTE increases exponentially with age.1 Various associated factors, such as heart failure, postoperative states, malignancy and long-term immobility, contribute towards the higher incidence of these disorders among elderly patients. In addition to VTE, arterial thromboses such as coronary artery disease and cerebrovascular disease are important clinical problems in this age group. Whereas the association of VTE with underlying thrombophilic disorders has been established unequivocally, their association with arterial thrombosis is not as clear. Furthermore, the indications and optimal cost-effective laboratory work-up is not as clear in older patients. The purpose of this article is to discuss the clinical significance of inherited thrombophilic disorders in older patients.

Pathophysiology of Thrombosis

In normal situations, a balance exists among the procoagulant, anticoagulant and fibrinolytic components of the haemostatic system. Thrombin is released as a result of vascular injury. Circulating thrombin (procoagulant), when bound to thrombomodulin on the endothelial surface, activates protein C to activated protein C (APC). APC is a serine protease with strong anticoagulant property that prevents excessive clot formation by inactivating factors V and VIIIa. Deficiency of naturally occurring anticoagulants (protein C, protein S and antithrombin) or resistance to inactivation by these anticoagu-

Inherited Hypercoagulable Disorders

The most commonly identified genetic thrombophilic disorders include:
1. activated protein C resistance / factor V Leiden;
2. antithrombin deficiency;
3. protein C deficiency;
4. protein S deficiency;
5. prothrombin gene abnormality;
6. hyperhomocysteinemia (may be inherited or acquired).

Activated Protein C Resistance/Factor V Leiden

As described above, APC limits the thrombus formation by inactivating factors Va and VIIIa. In 1993, Dahlback, et al. described the phenomenon of resistance to APC in a patient with strong personal and family history of thrombosis.2 The addition of APC to this patient’s plasma did not prolong activated partial thromboplastin time (aPTT) as expected. Subsequently, it was shown that the phenotype of APC resistance (APCR) was associated with a point mutation in the factor V gene at position 506.3 This mutation is named factor V Leiden, after the city in which it was first described. The factor V Leiden (FVL) mutation contributes to more than 95% of cases of APCR.4 APCR is the most common inherited cause of thrombophilia and is present in approximately 20% of unselected patients with thrombosis.5 The relative risk of thrombosis for carriers of FVL mutation is seven-fold for heterozygotes and 80-fold for homozygotes.6

In a prospective study of healthy men, the incidence rate of venous thrombosis in heterozygous carriers of the FVL mutation was found to increase significantly with age compared to individuals who did not have this mutation.7 This difference was greater in men older than 70 years of age. Another study of patients 70 years and older with one previous proven episode of thrombosis reported 11.6% incidence of FVL mutation in the elderly population (age range 70–102 years).8 These data suggest that it is reasonable to screen older patients with first VTE for FVL mutation.

Whereas FVL mutation is an established cause of venous thrombosis, vari-
ous studies on both young and older patients have failed to show any association between arterial disease and FVL mutation.9,12 Based on this evidence, routine screening for FVL mutation is not recommended for patients with myocardial infarction or ischemic stroke.

**Deficiencies of Antithrombin, Protein C and Protein S**

Antithrombin (AT; formerly AT III) is a serine protease anticoagulant. In the general population, the frequency of AT deficiency is estimated to be between 1:2,000 and 1:5,000.13 This is an autosomal dominant disorder and more than half of patients known to be deficient in AT will develop VTE over their lifetime. Most cases will have a first VTE between 15 and 35 years of age, and no cases have been reported after age 60.14 The prevalence of VTE and arterial thrombosis for AT-deficient patients in this study was 51% and 2%, respectively.

Protein C and protein S are vitamin K-dependent glycoproteins, and their deficiencies lead to a tendency to develop VTE. Approximately half the patients with protein C or protein S deficiency will have venous thrombosis by age 40–45 years. In a study with comprehensive thrombophilia testing, no cases of hereditary deficiency of AT, protein C or protein S were found in patients 70 years and older.8 Therefore, it seems reasonable to omit the diagnostic tests for deficiencies of AT, protein C and protein S in patients with first episode of VTE after age 45 and in the absence of a family history of thrombosis. The role of these thrombogenic abnormalities in arterial thrombosis is not clear.

**Prothrombin Gene Abnormality (Factor II G20210A)**

A mutation in the prothrombin gene at position 20210 results in higher levels of prothrombin and has been associated with increased risk of venous thrombosis. This mutation is present in approximately 1–2% of the Caucasian population.15 It has previously been shown that the coexistence of FVL and prothrombin gene mutation results in increased tendency for recurrent deep vein thrombosis (DVT).16 In this study, median and mean ages of first DVT in carriers of both these mutations were 29 and 32 years, respectively. From the available literature, there is no strong reason to justify the screening for prothrombin gene mutation in older patients.

No association has been established between the increased risk of arterial thrombosis and prothrombin gene mutation.17

**Hyperhomocysteinemia**

Homocysteine is a sulphur-containing amino acid formed during the metabolism of methionine. Various genetic and acquired deficiencies can result in increased homocysteine levels (see article, page 24, Table 2). The presence of hyperhomocysteinemia is strongly associated with increased risk of both venous18 and arterial thrombosis.19-22 The mechanism by which hyperhomocysteinemia leads to thrombosis is not clear, but is thought to be related to injury to endothelium.23

The prevalence of hyperhomocysteinemia is 5.7–36% in patients with thrombosis compared to 2.5–10% in the general population.23 Furthermore, increased prevalence (29.3%) of high homocysteine levels has been reported in elderly patients even without thrombosis.24 Vitamin supplementation can normalize homocysteine levels in most patients. Given the increased prevalence of high homocysteine levels among the elderly and the potential for therapeutic intervention, screening for hyperhomocysteinemia should be included in the work-up of elderly patients with hypercoagulable disorders.

Apart from these disorders, several other less frequent disorders have been associated with hypercoagulable states, including plasminogen deficiency, heparin cofactor II deficiency, dysfibrinogenemia, increased activation of factor XIII and elevated factor VIII. Further research and data are needed to evaluate the roles of these less common disorders in the routine clinical work-up for thrombophilia.

**Interaction of Inherited and Acquired Risk Factors**

Apart from APC resistance and hyperhomocysteinemia, the inherited thrombophilic disorders are rare in older patients, whereas acquired risk factors may be more clinically relevant in the elderly. Venous or arterial thrombosis could be the initial manifestation or complication of various medical disorders that are commonly seen among elderly patients, such as myeloproliferative disorders,
antiphospholipid syndromes and malignancy. Apart from these medical disorders, certain high-risk situations, such as orthopedic surgery, morbid obesity, prolonged immobilization and use of hormone replacement therapy, can increase the risk of venous thrombosis in elderly patients.

The pathogenesis of venous thrombosis is multifactorial and requires the interaction between congenital and acquired risk factors. The combination of an inherited risk factor with an acquired risk factor can result in the multiplication of risk for thrombosis.

**Evaluation of Hypercoagulable States in Elderly**

The clinical evaluation of elderly patients for thrombophilia should include a comprehensive medical history, thorough physical examination, routine laboratory investigations and a chest X-ray (Figure 1). Based on this initial evaluation, further work-up should be individualized. When a relevant history is present or when results of initial assessments are positive, appropriate investigations for underlying occult malignancy should be performed. Routine, aggressive search for occult malignancy in patients with primary venous thrombosis is not recommended. Other acquired causes of thrombophilia, such as antiphospholipid syndrome that is linked to both venous and arterial thrombosis, may also be relevant in older patients.

On the basis of available evidence, it is reasonable to screen older patients with first venous thrombosis for inherited risk factors such as APC resistance or FVL and hyperhomocysteinemia. There is no role for routine screening of FVL for arterial thrombosis. Hyperhomocysteinemia also is an important risk factor for arterial thrombosis. Whereas hyperhomocysteinemia is a treatable risk factor, knowledge of FVL status may alert to the need for thromboprophylaxis in high-risk situations. Testing for other genetic abnormalities should be done only in a select subgroup of patients with a relevant family history.

### References