EDUCATIONAL COMMENTARY – FACTOR V LEIDEN

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LEARNING OUTCOMES

On completion of this exercise, the participant should be able to

- describe the mechanism of thrombophilia due to factor V Leiden.
- explain the risk factors for thrombophilia associated with factor V Leiden.
- identify differences in homozygotes and heterozygotes for factor V Leiden.
- describe laboratory testing for factor V Leiden.

Introduction

The Factor V Leiden mutation is the most common inherited cause of thrombophilia, a disorder in which there is an increased tendency to form a thrombus, or clot.\(^1\) Thrombophilias may be inherited or acquired. Often thrombophilia is the result of a combination of inherited and acquired risk factors. Examples of acquired risk factors for thrombophilia are trauma, immobility, prolonged travel, obesity, metastatic cancer, pregnancy, oral contraceptives, hormone replacement therapy, and aging.

Normally, hemostasis is maintained by a balance between factors that promote clotting and naturally occurring inhibitors of clotting. When this system becomes out of balance, the result may be either bleeding or thrombosis. In persons with factor V Leiden (FVL), the scale is tipped toward the clotting side due to a genetic defect. Factor V Leiden has a prevalence of 3% to 7% in the general U.S. population, with the greatest percentage in persons of European heritage.\(^2\) In patients with venous thromboembolism, the prevalence of FVL is 50%.\(^1\)

Pathophysiology

Natural inhibitors of coagulation such as antithrombin, protein C, and protein S are present to help keep the hemostatic balance. Protein C is activated by thrombin. Activated protein C (APC) is a normal component of blood that contributes to antithrombotic surveillance mechanisms and prevents thrombosis. It inhibits coagulation by degrading activated factor V and activated factor VIII. Levels of APC are
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increased as a protective mechanism when large amounts of thrombin are generated, such as in disseminated intravascular coagulation.\(^3\)

An inherited disorder due to resistance to APC was recognized in 1993 and named *activated protein C resistance* (APCR). Approximately 90% of cases of APCR result from a single point mutation on the factor V gene.\(^4\) The precise genetic mutation was reported about a year later from studies performed in Leiden, the Netherlands: hence the name *factor V Leiden*. The mutation results from a substitution of glutamine for arginine at position 506 in the protein. This is one of three sites where APC normally cleaves activated factor V, inactivating it. The APC cleavage site is altered by this mutation, resulting in a factor V molecule that is resistant to APC inactivation.\(^5\)

**Clinical Findings**

Deep and superficial venous thromboses are the most common presentations of this disorder. Primary pulmonary embolism is less frequent in persons with FVL than in patients with other inherited disorders, such as deficiencies of antithrombin, protein C, or protein S.\(^3\)

Factor V Leiden inheritance is autosomal dominant. Therefore, it may be heterozygous (one factor V gene with the Leiden mutation and one normal gene) or homozygous (both factor V genes have the Leiden mutation).

Persons who are heterozygous for FVL have a two-fold to ten-fold increased lifetime relative risk for developing a venous thrombotic event. The risk is further increased if the person also has one or more acquired risk factors, such as pregnancy or use of oral contraceptives. By itself, FVL does not appear to increase the risk for arterial thrombosis, such as heart attack or stroke.\(^1\) Recurrent miscarriage is associated with having the FVL mutation, and one study reported that 20% of second-trimester pregnancy loss is due to the Leiden mutation.

Homozygous carriers of the FVL mutation are estimated to have a 20 to 50 times higher risk for a venous thrombotic event.\(^1\) Most homozygous carriers experience a venous thrombotic event before 40 years of age, but some can live without a clotting problem until they are 60 or 70 years old. Others may remain asymptomatic for life.\(^2\)

**Laboratory Testing**

Testing for FVL uses either the clot-based APC sensitivity test or a molecular technique. The most cost-effective approach is to use the coagulation test first and confirm with polymerase chain reaction-based molecular testing. Although the molecular test is often expensive and time-consuming, it is usually
necessary to confirm FVL, because 10% of patients with APCR do not have FVL. In addition, only the molecular test can distinguish heterozygotes from homozygotes.

The basis of the coagulation test is inhibition of activated factor V by APC; as a result the clotting time is prolonged. Activated protein C is added to the patient’s plasma and the activated partial thromboplastin time (aPTT) test is performed. Patients with the FVL mutation will have an aPTT value prolonged to a lesser amount than normal pooled plasma. In the modified APC sensitivity test, the patient’s sample is prediluted with factor V-deficient plasma to eliminate the effect of lupus anticoagulants and factor deficiencies that could prolong the baseline clotting time. Heparin is inactivated by polybrene. This diluted plasma can be used to run either an aPTT test or a tissue factor-dependent factor V assay. The modified (prediluted) APC sensitivity test is nearly 100% sensitive and specific for FVL.

Treatment

Patients with FVL are treated the same as any patient with a thrombosis. Patients with acute conditions are given heparin for at least five days, followed by oral anticoagulation with warfarin or a similar drug. Long-term anticoagulation is not usually necessary for heterozygotes unless they experience more than one thrombotic event or experience life-threatening thromboembolism. Asymptomatic patients with FVL should not be treated, but female patients should be informed about how pregnancy, oral contraceptive use, and hormone replacement therapy can increase risk. High-risk situations such as major surgery may require prophylactic anticoagulant drugs. Patients who are homozygous for FVL and experience a venous thrombotic event should be considered for long-term anticoagulation.

References


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