

Factor V Leiden Mutation

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Venous thromboembolism, the third most common cardiovascular disorder after ischemic heart disease and stroke, is associated with more than 300,000 hospitalizations and 50,000 fatalities annually in the United States.¹ Until recently, the majority of these thrombotic events had no identifiable cause.

In 1993, Dahlback² described a laboratory coagulation defect (ie, a poor anticoagulant response to activated protein C [APC]) in several families with inherited thrombotic tendencies.³ Subsequently, a mutation was identified on the factor V gene of the clotting cascade that accounted for 90% to 95% of all patients with APC resistance. This factor V mutation leads to a prothrombotic state, resulting in a seven- to 10-fold increase in the risk of thrombosis in heterozygotes and a 79-fold increase in the risk of thrombosis in homozygotes compared with the general population.⁴

The factor V Leiden mutation is estimated to be present in approximately 6% of the United States population, making factor V Leiden mutation at least 10 times as common as other genetic defects that cause thrombosis.⁴ Clinical symptoms in patients with the factor V Leiden mutation are variable. Some patients never experience thrombosis, whereas other patients suffer recurrent and severe thrombotic events. Because of this marked variance, lifelong anticoagulation may not be necessary for all individuals with factor V Leiden mutation.

This article presents a case of factor V Leiden mutation in a 19-year-old woman. Pathophysiology, epidemiology, diagnosis, clinical manifestations, and treatment are also discussed.

CASE PRESENTATION

A 19-year-old woman presents to the emergency department complaining of pain and swelling of 7 days' duration in her right leg. The patient is 4 weeks postpartum, having delivered a healthy baby through normal, spontaneous, vaginal delivery. The patient denies trauma and history of prior thrombosis. The patient reports having back surgery for scoliosis with rod placement 7 years before her current presentation; no postoperative complications occurred. Her family history reveals that her father had been hospitalized for "thick blood,"

which required a blood thinner, and her sister developed a postpartum deep vein thrombosis (DVT).

The patient is admitted to the hospital. Venous Doppler ultrasonography confirms a DVT in the popliteal vein and through the entire length of the femoral vein. The patient's laboratory studies indicate that lupus anticoagulant, protein C, protein S, antithrombin III, and anticardiolipin antibodies are all within normal limits. The patient is placed on heparin for 7 days and warfarin for 6 months.

Six months after the patient's initial presentation and 3 weeks after discontinuing warfarin, the patient experiences another DVT and is readmitted to the hospital. The patient's APC ratio is 1.8. DNA testing reveals that the patient is heterozygous for the factor V Leiden mutation. She is placed on lifelong warfarin therapy. Despite maintaining an international normalized ratio between 3 and 4, the patient experiences 10 subsequent episodes of DVT.

DISCUSSION

Pathophysiology and Epidemiology

The protein C system is a crucial anticoagulant pathway. In intact vessels, thrombin activates the protein C pathway by binding to thrombomodulin, an endothelial cell transmembrane protein. When thrombin binds to thrombomodulin, thrombin is converted from a procoagulant into an anticoagulant protease that cleaves and activates circulating protein C. APC, when aided by cofactor protein S, inactivates membrane-bound factors Va and VIIIa, two major procoagulants. Because of the ability to inactivate these proteins, the protein C pathway is a critical regulatory mechanism that limits clot formation.³

In 1995, Dahlback⁵ discovered that factor V actually plays two roles in the protein C pathway. In addition to being a precursor to procoagulant factor Va, factor V as well as protein S also function as cofactors to APC.⁵

In most patients, APC resistance is caused by a single base pair substitution in the gene coding sequence for clotting factor V. This substitution of glutamine for

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arginine at position 506 is termed *factor V Leiden mutation*. Factor V Leiden mutation alters the APC cleavage site of factor V and produces a factor Va molecule that cannot be properly inactivated by APC. The abnormal factor Va is not completely resistant to APC, but instead is inactivated at a rate 10 times slower than normal factor Va. The altered factor Va molecule is no longer degraded properly by APC. Therefore, the delicate balance between anticoagulant forces and procoagulant forces is disrupted, favoring thrombosis.⁶

Factor V Leiden can be transmitted through an autosomal dominant mode of inheritance. Heterozygote or homozygote status does not significantly differ according to gender. Multiple studies have provided evidence that all carriers of the factor V Leiden mutation are descended from a common ancestor.⁷⁻⁹ The highest prevalence of the mutation is found in Europe, most notably in Cyprus, Sweden, and Germany.⁸ The mutation also occurs in high levels in Saudi Arabia and in Arab and Jewish populations of Israel.⁸ Factor V Leiden mutation has not been found in the Chinese or southeast Asian populations. In the United States, the mutation is more commonly found in whites than in minorities.

Diagnosis

Tests for the diagnosis of factor V Leiden mutation include two functional clotting tests for APC resistance, an original assay and a modified assay, and DNA testing. Current recommendations for diagnosis include screening for APC resistance by functional assay first, followed by DNA testing if the APC resistance ratio is low or indeterminate.

In the original assay method, the responsiveness of plasma to APC is measured in terms of activated partial thromboplastin time (aPTT) (ie, the ratio of two aPTTs: the first aPTT in the presence of APC and the second aPTT in the absence of APC). The APC resistance original assay is accurate only when the following criteria are met: the patient is not on anticoagulants or estrogens, the sample is handled properly, and no lupus anticoagulant or other pre-existing coagulopathy is present. By using the cutoff values of 2.8 for men, 3 for women not taking oral contraceptives, and 2.5 for women taking oral contraceptives, the sensitivity of this test is 84% and the specificity is 95%.¹⁰

Cost (\$20 to \$75) and ease of performance are two advantages of the APC resistance original assay test. The original assay is sensitive for APC resistance caused by factor V Leiden mutation, but may also be positive in cases of other causes of APC resistance. False-positive APC resistance without factor V Leiden mutation can often be found in pregnant women, surgical patients,

and women taking estrogen. APC resistance can also cause false-positive results on the protein S test; thus, a complete thrombotic work-up must be performed in all APC-resistant individuals.

A modification of the original APC resistance test, in which the patient's plasma is diluted with factor V-deficient plasma, improves the sensitivity and specificity for detection of the Leiden mutation to 100%. The modified assay is not affected by variations in plasma handling and may be performed on patients taking anticoagulants. As the plasma sample is diluted with factor V-deficient plasma, all coagulation factors except factor V are present in sufficient amounts. As a result, individuals with APC resistance caused by other genetic abnormalities are not detected by the modified method. Therefore, most researchers suggest using the original and modified tests in tandem.

DNA testing is the gold standard in the diagnosis of factor V Leiden mutation. Unfortunately, DNA testing is costly (\$100 to \$200), laborious, and not routinely available.

Screening

One of the most controversial issues in the study of the factor V Leiden mutation is determining which patients should be tested. Women with factor V Leiden mutation who take oral contraceptives have a 35-fold increased risk for thrombosis. However, routine screening for this mutation before prescribing oral contraceptives would deny effective contraception to approximately 5% of women, while preventing only a small number of fatal pulmonary emboli.¹¹ A personal and family history of DVT taken before prescribing oral contraceptives can identify patients with a hereditary tendency toward multiple venous thrombosis and may reliably indicate patients who should undergo laboratory screening. Reports have shown that one of the most powerful predictors of APC resistance is a family history of thromboembolism.¹⁰

A preliminary guideline to follow when determining which patients should be screened for factor V Leiden mutation includes: 1) patients with DVT or pulmonary embolism in Western countries; 2) first-degree relatives of thrombotic patients with APC resistance; and 3) patients known to carry other prothrombotic genetic abnormalities. Testing is not warranted in patients with arterial thrombosis. General screening before exposure to circumstantial risk factors (eg, surgery and pregnancy) is unnecessary.¹²

Clinical Manifestations

As mentioned earlier, heterozygous patients with factor V Leiden mutation have a seven- to 10-fold

increased relative risk of thrombosis and homozygous patients have a 79-fold increased relative risk.⁴ Heterozygous women with factor V Leiden mutation who take oral contraceptives have a 35-fold greater risk of thrombosis than the general population.⁴ Homozygotes experience thrombotic events at a much younger age than heterozygotes or patients who do not carry the gene (31, 44, and 46 years, respectively).¹³ Thrombosis is more frequent in women than in men. In all APC-resistant patients, the recurrence rates of thromboembolic events were higher than in the general population.

Several studies report that homozygous patients with factor V Leiden mutation lived well into adulthood before experiencing their first thrombotic event.^{13,14} Most patients had been exposed to high-risk situations without developing thrombosis.¹³ These data suggest that the formation of a symptomatic thrombosis requires other stimuli in addition to the factor V Leiden mutation.

In both heterozygous and homozygous patients, the most common clinical manifestation of factor V Leiden mutation is DVT in the calf or femoral veins. In rare cases, thrombosis occurs at an unusual site. Cerebral vein thrombosis, mesenteric vein thrombosis, and retinal central vein occlusions have all been reported.¹⁴ No statistically significant differences in the rate of progression to pulmonary embolism between factor V Leiden patients and the general population have been demonstrated. A study of a large cohort of healthy men showed no association between factor V Leiden mutation and increased risk for myocardial infarction or stroke.³ No studies have demonstrated a clear link between APC resistance and arterial thrombosis. APC resistance, however, is associated with recurrent second trimester abortions.

Treatment

The risk of thrombosis is not high enough to justify prophylactic anticoagulation in asymptomatic carriers of the factor V Leiden mutation, except perhaps short-term prophylaxis in high-risk situations. In one study, the mean length of time between interruption of anticoagulation and recurrence of a thrombotic event was 10 years (range, 9 months to 25 years).¹⁴ These data do not support routine long-term anticoagulation in patients after the first thrombotic event because the risk of bleeding can outweigh the benefit of treatment. Lifelong anticoagulation should be reserved for patients who experience two or more thrombotic events or a single life-threatening thrombosis. Known carriers of the factor V Leiden mutation should avoid oral contraceptives and receive DVT prophylaxis before major surgical procedures, regardless of age.

SUMMARY

The factor V Leiden mutation is the most common congenital prothrombotic disorder described. Although patients may have a 79-fold increased risk of thrombosis, lifelong anticoagulation should be reserved for patients that have experienced multiple thrombotic events or a single life-threatening thrombosis. **HP**

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