Case Report

Recurrent Venous Thromboembolism in a Patient with Heterozygous Factor V Leiden Mutation

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ABSTRACT

Objective: To report a patient case identifying risk for recurrent venous thromboembolism (VTE) associated with heterozygous Factor V Leiden mutation.

Case Summary: A 54-year-old Caucasian male was diagnosed with heterozygous Factor V Leiden mutation in 2008 after experiencing a deep vein thrombosis (DVT) and bilateral pulmonary embolism. The patient was treated appropriately and started on anticoagulation therapy with warfarin through an anticoagulation management clinic. After approximately 17 months of warfarin therapy without incident, warfarin was discontinued. Within 2 months after discontinuation of anticoagulation therapy, the patient experienced his second DVT and left pulmonary artery embolus.

Discussion: The risk of recurrent venous thromboembolism (VTE) in patients with heterozygous Factor V Leiden mutation is documented as an approximate 1.4-fold increase compared to patients without thrombophilia. However, the risk increases dramatically when nonreversible (age) or reversible risk factors (obesity, smoking, and long air flights) are present in this population.

Conclusion: Based on recent literature, heterozygous Factor V Leiden mutation exponentially increases the risk of recurrent VTE, especially in the presence of other risk factors. Health care providers should complete a comprehensive review of the patients' other risk factors when deciding on duration of anticoagulation therapy for patients with positive heterozygous Factor V Leiden mutation.

Key Words—heterozygous Factor V Leiden mutation, venous thromboembolism, warfarin

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Venous thromboembolism (VTE) is a major medical issue that results from a combination of genetic, acquired, and modifiable risk factors.¹ Patients with VTE have a higher incidence of death compared to patients without VTE.² Thrombophilias have been associated with an increased risk of first and recurrent VTE, with Factor V Leiden mutation being the most common genetic risk factor.³ Factor V Leiden mutation occurs in 40% to 50% of cases of hereditary thrombophilia; only 3% to 8%

of the US population are heterozygous for the trait.⁴ Even though thrombophilias may increase the risk of VTE, current literature states that thrombophilia should not be considered a major factor in determining the duration of anticoagulation therapy after VTE. The guidelines state that standard therapy (3 to 12 months) of anticoagulation is acceptable in the prevention of recurrent VTE in patients with thrombophilias including Factor V Leiden mutation.⁵ Our case report documents a patient with heterozygous

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Factor V Leiden mutation who experienced recurrent VTE within 2 months after discontinuation of anticoagulation treatment.

CASE REPORT

A 54-year-old Caucasian male (height 72 in., weight 220 lbs, body mass index [BMI] 30 kg/m²) was diagnosed with idiopathic VTE (right popliteal/posterior tibial deep vein thrombosis [DVT] and bilateral pulmonary embolism) in April 2008. He reported a past surgical history of a bullet removal from the right knee (1976) and a minor facial repair secondary to a knife wound (1985). Patient's social history was positive for tobacco use (30 pack-years) and occasional alcohol use on weekends. A hypercoagulable work-up identified a heterozygous Factor V Leiden mutation. He was treated appropriately and referred to the anticoagulation management clinic for warfarin (*Coumadin*) therapy to achieve a target international normalized ratio (INR) goal of 2 to 3. The patient was also diagnosed with dyslipidemia during the 2008 hospital admission and started on atorvastatin (*Lipitor*) 10 mg and fenofibrate (*Tricor*) 145 mg daily. He was continued on warfarin for approximately 17 months with greater than 57% of readings within target goal. During the 17 months, the patient did not experience any adverse events, bleeding, or VTE. In September 2009, warfarin was discontinued after a lengthy discussion with his physician regarding benefit versus risk and utilizing recommendations from the guidelines.

In November 2009, the patient presented to the family practice clinic complaining of left leg swelling, pain, and shortness of breath for the past several days after an approximately 6-hour airline flight. He was admitted to the hospital with new large, left partial-occlusive pulmonary artery emboli (documented by a spiral CT) and left lower leg extremity DVT (documented by an ultrasound). At that time, his past medical history was consistent with prior VTE plus recurrent kidney stones and spinal arthritis. In addition, the patient had quit smoking in 2008 after first VTE and denied any recent tobacco use. Aspirin was the only home medication. A second hypercoagulable work-up was performed, which confirmed the heterozygous Factor V Leiden mutation and was not positive for any other hypercoagulable defect. He was treated with enoxaparin and warfarin therapy during the admission and referred to the anticoagulation management clinic for warfarin therapy. He has been treated with warfarin and monitored in

the anticoagulation management clinic without any adverse events or subsequent VTE since 2009.

DISCUSSION

According to the 2008 and 2012 guidelines for anticoagulation management, the presence of hereditary thrombophilia (eg, Factor V Leiden mutation) is not a major risk factor in determining the duration of anticoagulation. Based on these guidelines, duration of 3 months or 6 to 12 months is appropriate. The guidelines state that a combination of risk factors (reversible plus hereditary) may pose an increased risk for a second VTE after discontinuation of anticoagulation therapy.^{1,5} However, the duration of anticoagulation needed to prevent further VTE is unclear.

Removal of anticoagulation in itself is associated with theoretical concern about increased harm. The guidelines mention that this harm is evident in the first 8 to 9 weeks post discontinuation of anticoagulation therapy. However, the studies have inconsistent results and have measured secondary markers instead of recurrent VTE events. In essence, the guidelines suggest that this harm is due to an unmasked prothrombotic state instead of a rebound effect.⁶ Our patient presented with his second VTE within the 9-week time frame.

Several studies including the Leiden thrombophilia study did not find an increased risk for VTE in patients with heterozygous Factor V Leiden defect.⁷⁻⁹ However, systematic reviews found an increased risk of approximately 1.56 and 1.46.^{10,11} Based on the studies, risk of recurrent VTE with only the mutation is approximately 1.4 to 1.6 compared to patient without thrombophilia.^{1,4} Despite the documented low risk of recurrent VTE, our patient had another event. The literature is unclear whether the Factor V Leiden heterozygous mutation has a super-additive effect in the setting of reversible risk factors compared to the normal population with only the reversible risk factors. Newer studies since 2009 have added more information about determining the risk of heterozygous Factor V Leiden mutation in the setting of reversible risk factors.

Long-haul airline flights (greater than 8 hours) have been documented as a mild risk factor (2-fold) of recurrent VTE.^{1,12} However, in the setting of Factor V Leiden mutation, an 8-fold increase was seen in patients who traveled 4 hours or more by bus, car, or train. The risk was higher (13.8%) in patients with documented thrombophilia mutation and air travel (greater than 4 hours).¹³ Another study looking at long-haul flights demonstrated the risk of VTE as

16-fold in patients with Factor V Leiden mutation.¹⁴ The studies included both heterozygous and homozygous patients but did not delineate the actual number of heterozygous participants. Clearly, our patient had an increased risk of recurrent VTE associated with his flight of approximately 6 hours.

Cigarette smoking and the risk of VTE have also been studied. The Tromsø study identified an increased risk of 1.5 of total VTE and 1.8 in provoked VTE in heavy smokers (>20 pack-years).¹⁵ Heavy smokers showed a higher incidence of VTE compared to nonsmokers or moderate smokers when combined with the heterozygous Factor V Leiden mutation.¹⁶ Smoking may have contributed to our patient's first VTE (2008), but it could not have been a contributing factor with his second VTE because he quit smoking in 2008.

In the Multiple Environmental and Genetic Assessment of risk factors for VTE (MEGA study), overweight (BMI 25-29.9 kg/m²) and obesity (BMI ≥30 kg/m²) were associated with 1.7- and 2.4-fold increase in VTE compared to healthy weight individuals (BMI <25 kg/m²), respectively. A 7.9-fold increase was seen in VTE when Factor V Leiden mutation and obesity were combined compared to healthy weight noncarriers.¹⁷ In the Danish prospective Diet, Cancer and Health study, Severinsen et al identified an increased risk of VTE in overweight and obese patients with the heterozygous Factor V Leiden mutation compared to healthy weight individuals without the mutation. In addition, the incidence of VTE increased as the weight of patients with the genetic mutation increased compared to healthy weight individuals with the genetic mutation.¹⁶ Our patient's BMI of 30 kg/m² should be considered a factor contributing to his recurrent VTE, especially in the setting of heterozygous Factor V Leiden mutation.

Other risk factors associated with a significant increase in the risk of recurrent VTE when combined with a positive Factor V Leiden heterozygotes mutation are hyperhomocysteinemia, oral contraceptives, pregnancy, minor injury, non-O blood type, age (>60 years old), and malignancy.^{4,18,19} These risk factors should be taken into consideration; however they did not apply to our patient case.

Regarding mortality associated with thrombophilia, one study revealed no increase in mortality for patients with inherited thrombophilia and history of thrombosis. Of the patients, approximately 27% had a Factor V Leiden mutation (both homozygous and heterozygous). However, patients were allowed anticoagulation therapy during the study.²⁰

A retrospective survival analysis of approximately 1,900 patients with classical hereditary thrombophilia risk factors showed no major impact on long-term survival in patients with VTE, except for patients with hyperhomocysteinemia.²¹ However, more than 21% of patients with thrombophilia were on anticoagulation therapy for longer than 18 months. The studies showed no increase in mortality with Factor V heterozygous mutation, but the mortality rate with or without anticoagulation therapy is still unclear.

CONCLUSION

Based on recent literature, heterozygous Factor V Leiden mutation exponentially increases the risk of recurrent VTE especially in the presence of other risk factors. Patient education about the modifiable risk factors (eg, obesity, travel, smoking) are essential for patients with heterozygous Factor V Leiden mutations to reduce the added risk of recurrent VTE, although the duration of effective anticoagulation therapy after first VTE for patients with a positive heterozygous Factor V Leiden mutation in the presence of other factors is still unclear. Based on our patient case report, health care providers should complete a comprehensive review of the patient's other risk factors when deciding on duration of anticoagulation therapy for patients with positive heterozygous Factor V Leiden mutation and potentially consider long-term anticoagulation due to an increased risk of recurrent VTE when additional risk factors are present.

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