CLINICAL VIGNETTE

Prothrombin G20210A Mutation and Venous Thrombosis

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A 63-year-old male with elevated fasting glucose was traveling and noted edema in his right lower extremity prompting urgent care evaluation in New York. He had a prior right deep vein thrombosis 15 years before and was not taking aspirin or chronic anticoagulants. Venous Doppler confirmed thrombosis in the deep venous supply of the right leg proximal to the knee. He was treated with enoxaparin with bridging to warfarin. He presented to my office four weeks later off anticoagulants.

He is currently a light cigar smoker with prior history of smoking 1 pack of cigarettes per day for 10 years back in the 1970's. He averages about 1 glass of wine/day and exercises regularly. Family history is negative for coagulation disorders.

Vital signs included height of 5 foot 11 inches, weight 185.8 pounds, BMI is 25.9, blood pressure 116/74, pulse 60 and normal temperature. Examination was normal except for mild right leg edema.

Labs included normal CBC, chemistries, thyroid function, lipid panel, PSA, PT, PTT and ESR. Hypercoagulability testing was normal for protein C, protein S, anti-thrombin 3, factor V Leiden, and Lupus anti-coagulant but positive for the prothrombin G20210A mutation.

There are many genetic and environmental factors that contribute to an increased risk for venous thrombosis including protein C deficiency, protein S deficiency, factor V Leiden, anti-phospholipid antibody syndrome, Lupus anticoagulant, pregnancy, trauma, malignancy, and various medications. Along with factor V Leiden, the prothrombin G20210A mutation (also called prothrombin mutation or factor II mutation) is one of the most common genetic causes of hypercoagulability[1]. Factor V Leiden and prothrombin G20210A mutation account for approximately half of all genetically related cases of thrombosis[1]. Prothrombin G20210A mutation was first described in 1996 and is common in certain populations with between 1-6% of the Caucasian population having at least one copy of the mutation while quite rare among African Americans, Asians and native Americans[2]. The mutation is particularly common in Ashkenazi Jews of European descent and is especially common in those from the Mediterranean region and Mexico[3]. Between 10-15% of European Caucasians with venous thrombosis test positive for this mutation while 1-5% of healthy similarly matched controls test positive[4]. Approximately 25% of all thromboses have a genetically defined factor so testing is often indicated[2]. Most patients who test positive for the prothrombin G20210A mutation are heterozygote for the gene with uncommon homozygote cases[3].

Prothrombin G20210A mutation is associated with increased levels of prothrombin which is believed to be the cause of the increased clotting tendencies[5]. Prothrombin, also known as factor II, is the precursor for thrombin, which is responsible for converting fibrinogen to fibrin and is a critical part of the clotting cascade. Prothrombin is a vitamin K dependent factor and is directly involved in the coagulation cascade process so abnormal prothrombin can quickly and significantly impact the risk of coagulation[6]. One study showed a doubling of the prothrombin level was associated with a doubling of the risk of venous thrombosis[1]. Prothrombin G20210A mutation does not appear to significantly impact the structure or function of prothrombin but does increase the circulating levels, most likely through increased mRNA production[7]. The mutation is located on the non-coding part of the prothrombin gene with an adenine replacing a guanine at position 20210, which affects mRNA production and leads to attachment of a poly-A tail leading to elevated prothrombin levels[7]. A 15% increase in prothrombin levels has been shown to increase the risk of venous thrombosis[7]. Other studies have shown that this mutation can lead to decreased levels of thrombin-activatable fibrinolysis inhibitor (TAFI), which is an inhibitor of fibrinolysis[8]. Increased prothrombin and reduced fibrinolysis are believed to be the main factors for increased venous thrombosis. Patients with the prothrombin G20210A mutation have approximately a 2-3 fold increased risk of thrombosis[9]. In comparison, those with protein C deficiency or protein S deficiency have a 5-10 times increased risk of thrombosis.[9]

In addition to increased risk of venous thrombosis, those with the prothrombin G20210A mutation also have a 30% increased risk of coronary artery

disease[10]. This risk is significantly increased in patients who smoke or take oral contraceptives[9]. For example, heterozygous carriers who take oral contraceptives have a 15-fold increased risk of venous thrombosis[9]. Patients with the prothrombin G20210A mutation also have an increased risk of a slow clinical response to anticoagulation. This poor response appears to be related partly to elevated prothrombin levels[11]. Thus, they may require a higher dose of anticoagulants and may be at higher risk of recurrent clots[11]. This is also important to consider in patients with other genetically associated hypercoaguable states such as protein C deficiency and anti-thrombin 3 deficiency.

Treatment and Prognosis

Treatment for clots in patients with the prothrombin G20210A mutation is similar to treatment protocols in normal patients, although the length of treatment may need to be extended depending on the specific risk profile of the patient[11]. Currently, there are no well-designed studies addressing the duration of anticoagulation with prothrombin G20210A mutation. Studies performed on populations with factor V Leiden found the bleeding risks associated with long term anticoagulation may outweigh the potential benefits of long-term anticoagulation[12]. Those at high risk of recurrent thrombosis, such as those with a prior history of clot or those with multiple identifiable risk factors, can be considered for long-term anticoagulation[12].

Clinical Course and Follow-Up

This patient with a right leg deep venous thrombosis was treated for six months with warfarin anticoagulation. After consultation with a hematologist, it was recommended that he remain on lifelong anticoagulation. He tested positive for the prothrombin G20210A mutation, this was his second episode of deep thrombosis, and he continued to smoke. Because of these three factors, he remains at high risk of recurrent thrombosis. He was again counseled on the importance of completely abstaining from smoking.

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