Provoked deep vein thrombosis and saddle pulmonary embolism in a pediatric patient with multiple genetic risk factors for venous thromboembolism

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Abstract

Heterozygous mutations in Factor V Leiden (FVL) or prothrombin G20210A (PT-G20210A) are relatively common; the presence of double-heterozygosity for these mutations is rare but may be as high as 5% in patients with deep vein thrombosis (DVT). Antiphospholipid syndrome (APS) is a rare autoimmune disorder and commonly presents in adolescents and young adults. This report describes the diagnosis, treatment, and outcome for acute presentation of extensive lower extremity DVT and saddle pulmonary embolism (PE) in a previously healthy 17-year-old male found to have multiple genetic risk factors including double-heterozygosity for FVL/PT-G20210A and concurrent APS, which is rare and not well-described.

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Abbreviations:

aβ2GPI	Anti-beta 2 glycoprotein I
aCL	Anti-cardiolipin
APS	Antiphospholipid syndrome
DVT	Deep vein thrombosis
EULAR	European Alliance of Associations for Rheumatology

aβ2GPI	Anti-beta 2 glycoprotein I
FVL	Factor V Leiden
GPI	Glycoprotein I
LA	Lupus anticoagulant
PE	Pulmonary embolism
PT-G20210A	Prothrombin G20210A

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Abstract Heterozygous mutations in Factor V Leiden (FVL) or prothrombin G20210A (PT-G20210A) are relatively common; the presence of double-heterozygosity for these mutations is rare but may be as high as 5% in patients with deep vein thrombosis (DVT). Antiphospholipid syndrome (APS) is a rare autoimmune disorder and commonly presents in adolescents and young adults. This report describes the diagnosis, treatment, and outcome for acute presentation of extensive lower extremity DVT and saddle pulmonary embolism (PE) in a previously healthy 17-year-old male found to have multiple genetic risk factors including double-heterozygosity for FVL/PT-G20210A and concurrent APS, which is rare and not well-described.

Introduction

The prevalence of a heterozygous mutation in either Factor V Leiden (FVL) or prothrombin G20210A (PT-G20210A) is 5% or 2%, respectively, in the Caucasian population. The prevalence of double-heterozygosity for these mutations is estimated to be 0.1% in the Caucasian population and may be as high as 5% in patients diagnosed with deep vein thrombosis (DVT). Heterozygosity for FVL increases the risk of venous thromboembolism (VTE) from 1:1 000 to 3-8:1 000 per year whereas heterozygosity for PT-G20210A mutation has been shown to increase the risk from 1:1 000 to 2-3:1 000 per year. Antiphospholipid antibody syndrome (APS) is a rare autoimmune disorder with estimated prevalence of 20-50 cases per 100 000 persons and most commonly presents in adolescents and young adults. These common polymorphisms are well established risk factors for VTE. More recently, there have been large studies comparing the risk in patients who have double-heterozygous states or multiple polymorphisms. One study found patients who are heterozygous for both FVL and PT-G20210A have up to a 20-fold increased risk for initial venous thromboembolism. The prevalence and associated risk of double-heterozygosity for FVL/PT-G20210A and concurrent APS is rare and not well-described.

This report aims to describe the diagnosis, treatment, and outcome for the acute presentation of extensive lower extremity DVT and saddle pulmonary embolism (PE) in a previously healthy 17-year-old Caucasian male found to have multiple genetic risk factors for venous thromboembolism.

Results

Case Description

The patient presented due to new onset chest pain and persistent left leg pain and swelling after a hyperextension injury of the knee 4 days prior forced him to be immobilized. He was tachycardic on presentation with otherwise normal vital signs. Physical examination was significant for left lower extremity swelling from knee to ankle with limited range of motion secondary to swelling and pain. Although he had erythematous skin changes on his ankle, he had palpable pulses and normal capillary refill. He had a normal cardiopulmonary examination. His known trauma, immobilization, and obese body mass index (34 kg/m^2) were considered possible etiologies to provoke the thromboses, and his family history was unremarkable for thrombosis. Doppler ultrasonography showed extensive occlusive thrombosis of left femoral and popliteal veins. May-Thurner syndrome was ruled-out given the limited proximal extent of the left leg thrombus and venous anatomy. Chest computed tomography angiography demonstrated saddle PE with thrombus extending into the left and right pulmonary arteries (Fig. 1). Echocardiogram showed no evidence of right

ventricular systolic failure or dilation, and brain natriuretic peptide and troponins were normal. He was hemodynamically stable and his PE was categorized as low-risk. No procedural interventions were indicated.

He was initially started on therapeutic anticoagulation with intravenous unfractionated heparin titrated to achieve anti-Xa level between 0.3-0.7 units/mL. He required oxygen support via nasal cannula but was weaned to room air within 48 hours of presentation. He was transitioned to enoxaparin at pediatric therapeutic starting dose of 1 mg/kg and titrated to achieve an anti-Xa level between 0.5-1 units/mL. Upon discharge, he still had swelling and pain of the lower extremity but was able to ambulate on crutches.

Despite his known preceding trauma, immobility, and obesity, he underwent laboratory evaluations for underlying thrombophilia due to the degree of thrombosis on presentation. Results were significant for heterozygous mutations of both FVL and PT-G20210A, positive anti-beta 2 glycoprotein I (aβ2GPI) IgG antibody, and lupus anticoagulant (LA; positive Staclot, negative diluted Russell viper venom time); his aβ2GPI IgM and anti-cardiolipin (aCL) IgM/IgG antibodies were all negative. He was discharged home on therapeutic enoxaparin due to concern for reduced efficacy of direct oral anticoagulants in treatment of patients with APS. Repeat testing at 3 months re-demonstrated the same findings for his antiphospholipid antibody profile, which was consistent with a diagnosis of APS based on the Sapporo criteria.Repeat Doppler ultrasonography at 3 months demonstrated improvement but residual non-occlusive thrombosis of left femoral and popliteal veins and therapeutic enoxaparin was continued.

Discussion

This 17-year-old Caucasian male's challenging presentation of DVT and saddle PE occurred in the setting of trauma, immobilization, obesity, and double-heterozygosity for FVL/PT-G20210A with concurrent APS. Given the persistence of his APS in the setting of double-heterozygosity for FVL/PT-G20210A, despite resolution of his previous provoking trauma and immobilization, he will be continued on therapeutic anticoagulation with enoxaparin for least 6 months.

The risks of VTE associated with either FVL or PT-G20210A mutations have been described in a multitude of studies. However, the risk in patients with double-heterozygosity for FVL/PT-G20210A has been more difficult to understand due to lack of power in many studies given the rarity of both polymorphisms together.[6] In the meta-analysis by Simone et al, the risk of initial VTE in patients with double-heterozygosity for FVL/PT-G20210A was increased when compared to patients without either mutation or with PT-G20210A heterozygosity alone.[7] There is conflicting evidence on VTE recurrence risk in patients with double-heterozygosity for FVL/PT-G20210A. An investigation in the Netherlands reported no increase in risk of VTE recurrence for patients with double-heterozygosity relative to patients without known FVL or PT-G20210A in a population in the Netherlands.[1] However, the relative risk of VTE recurrence was reported as high as 3.7 for patients with double heterozygosity compared to patients with a single FVL mutation in a population in Italy.[8] It has also been demonstrated that patients with double-heterozygosity for FVL/PT-G20210A may present with the first episode of VTE at a significantly younger age than patients with VTE associated with no genetic risk factors or single gene defects alone (34.7 vs 40.6 years, $P<0.01$). Despite some differing reports of recurrence risk, there is data to support the use of lifelong anticoagulation for patients with double-heterozygosity alone.

Our patient has the additional risk factor of APS, which with concurrent double heterozygosity of FVL/PT-G20210A has been described in at least one case of catastrophic antiphospholipid syndrome as a contributor to disease. For APS alone, there is conflicting evidence for the use of aspirin for primary prevention of arterial and venous thromboembolism, although The European Alliance of Associations for Rheumatology (EULAR) has recommended primary prevention for even asymptomatic patients with APS and a high-risk profile (presence of persistent LA or any combination of two or more of LA/aCL antibody/aβ2GPI antibody) with low-dose aspirin since 2019.[4,10] There is limited evidence for secondary prevention of venous thromboembolism in patients with APS, as would apply to our patient, but warfarin monotherapy is typically utilized with a target international normalized ratio of 2.0-3.0. In the event of recurrent venous thrombosis in a patient with APS while on warfarin, EULAR recommends consideration of warfarin combined with

low-dose aspirin or extended therapeutic enoxaparin.[4,10.] Family discussion regarding the benefits and risks of indefinite anticoagulation with warfarin after 6 months is ongoing for the patient in this case.

Much of the literature examining risk of VTE with genetic mutations specifically exclude individuals with inciting factors, such as trauma, which was an important provoking factor for this patient. This case also highlights the importance of evaluation for thrombophilia in patients in select circumstances with extensive thrombus burden, even in the setting of known risk factors such as trauma and obesity, as the results may have lifelong clinical implications.

Legend: FIGURE 1 Patient's chest computed tomography at initial diagnosis of saddle PE with thrombus extending into the left and right pulmonary arteries.

Conflict of Interest: The authors declare that there is no conflict of interest.**Acknowledgements:** We are grateful to Dr. Pamela Camacho for her clinical care of this patient.**References**

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