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Heterozygous Mutation of Factor V Leiden Complicating Venous Thromboembolic Syndrome: A Case Report

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Abstract **Case Report**

Factor V Leiden (FVL) is the most common hereditary thrombophilia, causing resistance to activated protein C (APC) and increasing the risk of venous thromboembolism (VTE). The coexistence of FVL and antiphospholipid syndrome (APS), an acquired autoimmune prothrombotic condition, is rare but can significantly heighten thrombotic risk. ***Case presentation:*** We report the case of a 32-year-old male presenting with an unprovoked deep vein thrombosis complicated by non-severe pulmonary embolism. The patient had no significant past medical or familial thrombotic history, but chronic smoking was noted. Laboratory evaluation revealed a heterozygous FVL mutation, resistance to APC, and a positive antiphospholipid profile. Imaging confirmed pulmonary embolism and thrombosis of the right popliteal vein. ***Discussion:*** The combination of hereditary (FVL mutation) and acquired (APS) thrombophilias creates a synergistic prothrombotic state. This rare association emphasizes the need for comprehensive thrombophilia work-up in young patients presenting with unexplained or recurrent VTE. Genetic and immunological investigations guide personalized anticoagulation strategies and familial screening. ***Conclusion:*** This case highlights the clinical relevance of identifying coexisting thrombophilic disorders. Early recognition and appropriate management are crucial to reduce recurrence and complications in patients with combined genetic and acquired risk factors for thrombosis.

Keywords: Factor V mutation (Leiden); hereditary thrombophilia; resistance to activated protein C; DVT; Genetic and coagulation.

1. INTRODUCTION

Factor V Leiden (FVL) is a genetic mutation of the factor V gene that leads to resistance to activated protein C (APC), a powerful inhibitor of the coagulation system. This mutation was discovered in 1994 by Professor Bertina's team. FVL is responsible for more than 90% of cases of APC resistance and is a common cause of hereditary thrombophilia in Caucasian populations. This mutation increases the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), especially in patients with other thromboembolic risk factors.

Antiphospholipid syndrome (APS), on the other hand, is an autoimmune disease characterised by the presence of antiphospholipid antibodies (APAs) that increase the risk of thrombosis. It is often associated with thromboembolic complications, both venous and arterial. The coexistence of APS and a Factor V Leiden mutation is rare, but can significantly increase the risk of thrombosis. This report describes a case of unprovoked deep vein thrombosis complicated by pulmonary embolism in a patient with a heterozygous Factor V Leiden mutation, without the presence of APS.

2. OBSERVATION

A 32-year-old male patient, single, with no history of diabetes or hypertension, but with a history of chronic smoking (15 pack-years), is hospitalised for a non-severe pulmonary embolism complicating an unprovoked unilateral deep vein thrombosis (DVT).

History and risk factors:

- Cardiovascular risk factors: chronic smoking, male gender.
- Thromboembolic factors: no trauma, recent surgery, prolonged immobilisation or family history of thrombophilia. The patient had travelled for 9 hours 24 hours before the onset of symptoms.

Clinical presentation: The patient presented with dyspnoea at rest and localised chest pain without radiation. Clinical examination revealed:

- BP: 131/80 mmHg, FC: 75 bpm, RR: 24 bpm, SaO2: 96%
- Normal cardiac auscultation, no murmurs or pericardial friction
- No signs of left or right ventricular failure
- No pain or signs of recurrence of DVT in the lower limbs

Investigations

- **Chest CT angiography**: bilateral segmental pulmonary embolisms with bilateral basal pulmonary infarction.
- **Venous Doppler ultrasound of the lower limbs**: thrombophlebitis of the right popliteal vein.
- A coagulation and thrombophilia assessment was performed:
- **Complete blood count (CBC):** WBC: 17.93 G/L, Hb: 15.4 g/dL, PLQ: 154 G/L.
- **Coagulation tests**: PT: 14.3 s, APTT: 34.9 s.
- **Protein C**: 49% (normal range: 70-140), Protein S: 94% (normal range: 60-140).
- **Resistance to activated protein C**: 71.3 s (normal range: 120-300).
- **Mutation screening**: no factor II mutation, presence of heterozygous factor V Leiden mutation.
- **Antiphospholipid profile (SAPL):** Positive

3. DISCUSSION

Antiphospholipid syndrome (APS) is an autoimmune disease that is more common in women of childbearing age or around the age of 40[1]. It is the most common cause of acquired thromboembolic disease, responsible for highly thrombophilic venous and arterial thrombosis [2], through various mechanisms:

- Disruption of the coagulation cascade (through decreased protein C activation and inhibition of β2-glycoprotein, antithrombin and fibrinolysis).
- Activation of endothelial cells (via increased expression of tissue factor and secretion of pro-inflammatory cytokines).
- Platelet activation (through increased synthesis of thromboxane A2).
- Formation of immune complexes between antiphospholipid antibodies (APA) and β2-glycoprotein I in the membrane phospholipids of endothelial cells and platelets [3].

An American cohort study, composed mainly of white patients (97%) newly diagnosed with APS between 2000 and 2015 in Olmsted County, Minnesota, reported an annual incidence of 2.1 per 100,000 inhabitants and an estimated prevalence of 50 per 100,000 [4].

These patients are at high risk of thrombotic recurrence, estimated at 29% in the first six months after discontinuation of anticoagulation [5].

Factor V is a cofactor in coagulation whose activity is inhibited by activated protein C (APC). APC is a powerful inhibitor of the coagulation system, cleaving the activated forms of factors V and VIII (FVa and FVIIIa). The factor V mutation, known as 'factor V Leiden' (FVL), was discovered in a patient from Leiden, the Netherlands. It is particularly common in populations of European origin. It is a point mutation in the factor V gene, transmitted in an autosomal dominant manner. It leads to the substitution of arginine by glutamine at position 506, which removes an APC cleavage site, making FVa less sensitive to inactivation, a phenomenon known as 'APC resistance' [6].

FVL is responsible for more than 90% of cases of APC resistance. Other causes of APC resistance include rarer genetic mutations (factor V Cambridge, factor V Liverpool), as well as acquired causes, notably antiphospholipid antibodies (APLA).

The prevalence of this mutation is estimated to be between 3% and 8% in Caucasian populations, compared to only 1.2% in African Americans. It is rarely found in indigenous African, Chinese or Japanese populations. Homozygosity for FVL occurs in approximately 1 in 500 to 1 in 1,600 individuals in Caucasian populations [9]. The high prevalence of this mutation in the general population could be explained by evolutionary advantages, such as reduced blood loss during childbirth or improved survival during episodes of sepsis [10].

The thrombotic risk associated with FVL varies depending on the genotype. Heterozygosity for FVL confers a 2.7-fold increased risk of developing venous thrombosis, while homozygosity increases this risk by a factor of 18 compared to a person without the mutation [11]. Other risk factors, such as age, smoking, obesity and oestrogen use, can further increase this risk.

Our patient presents with a combination of SAPL and a heterozygous mutation of factor V. The coexistence of these two conditions is rare, but it synergistically increases hypercoagulability, which can lead to a more severe thromboembolic presentation.

In the literature, very few cases document the association of SAPL with factor V mutation. Among the cases reported, one article describes a young patient with Libman-Sacks endocarditis and stroke, who carried a heterozygous mutation of factor V Leiden but had only suffered a transient ischaemic attack [12]. Two other cases report the association of SAPL with a homozygous FVL mutation in patients with Budd-Chiari syndrome [13].

This case highlights the importance of systematically screening patients with unusual thromboses, whether venous or arterial, in order to identify multiple underlying thrombophilic disorders. This allows for the optimisation of anticoagulation strategies, taking into account patients' personal and family histories.

Comparison with recommendations:

In comparison with international recommendations concerning the management of Factor V Leiden, several key points should be noted:

1. **Targeted screening for FVL**: DNA genotyping is recommended for patients with thrombosis, particularly in the presence of antiphospholipid antibodies. Our clinical approach is in line with this recommendation, thus justifying genetic testing in this context.
2. **Screening criteria**: It is recommended to test patients with thrombosis before the age of 50, recurrent thrombosis or thrombosis in unusual sites. Our patient meets these criteria, highlighting the relevance of screening.
3. **Family screening**: Screening of relatives who are carriers of the FVL mutation is recommended to avoid thromboembolic risks in the family. This could be considered in the management of our patient.
4. **Environmental factors**: Screening of women with thrombosis during pregnancy or on oral contraceptives is also recommended. In the case of our patient, this could be relevant for future management.
5. **Assessment of other thrombophilias**: Recommendations encourage screening for other thrombophilic mutations such as prothrombin 20210A in the presence of FVL. This additional assessment would help to avoid underdiagnosis of other potential thrombotic risks.
6. **Family and genetic implications**: Informing the patient and her family about the hereditary risks associated with the FVL mutation is essential for comprehensive care and adequate prevention of thromboembolic complications in the family.

4. CONCLUSION

The thrombotic risk associated with Factor II and V Leiden mutations has been well established, as confirmed by numerous scientific studies.

There are many recommendations and clinical-biological scores that can be used to assess a patient's thrombotic risk and decide whether or not to initiate thromboprophylaxis.

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