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Broadening the Factor V Leiden Paradox: Pulmonary Embolism and Multisystemic Arterial Thrombosis as 2 Sides of the Spectrum

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Abstract **Case Report**

Factor V Leiden mutation is an inherited disorder of coagulation. Factor V Leiden resists the effects of activated protein C, so it takes longer to turn off Factor V Leiden. As a result, clotting goes on longer than usual. It's associated with thrombotic events that classically involve the venous thrombosis and rarely arteries. However, the role of factor V Leiden in the genesis of arterial thrombosis is not yet fully understood. We report a case of a young woman with multiple thromboembolic events including pulmonary embolism, renal associated to hepatic infarction, apical thrombus on the left ventricle and ischemic stroke, in the context of a factor V mutation.

Keywords: Leiden mutation, pulmonary embolism, ischemic stroke, hepatic infarction, left ventricular thrombus.

INTRODUCTION

Resistance to activated protein C is a frequent cause of venous thrombosis. In 95% of cases, this resistance is related to a mutated factor V, pro-coagulant cofactor required for the transformation of prothrombin into thrombin, that becomes resistant to inactivation by protein C. The mutation is responsible for an abnormal phenotype of this factor, commonly referred to in these cases as factor V Leiden (FVL). The clinical presentation depends on the localization of the thrombus.

CASE REPORT

A 30-year-old woman was admitted to the hospital as an emergency for acute hemoptysis and dyspnea, which appeared during her 4th month postpartum. The patient was non-obese, with no particular cardiac history and at the time of admission presented signs of congestive heart failure.

Family history was negative for any thrombotic disease. Regarding past medical history the patient had no previous miscarriage, neither deep vein thrombosis, nor recent prolonged bed rest or hospital admissions.

She had tachycardia at 119 beats per minute, polypnea at 25 cycles per minute. Cardiac auscultation showed a diastolic murmur at the mitral and aortic areas, with signs of right cardiac decompensation, the vascular examination was normal.

The chest X-rays objective a cardiomegaly (cardiothoracic index = 0.65) with pleural effusion in the right diaphragmatic recess. On the electrocardiogram, he had sinus rhythm, left ventricular hypertrophy and secondary repolarization disorder.

Due to the high clinical suspicion, computed tomography pulmonary angiography was performed, which confirmed a bilateral pulmonary embolism Figure 1 of the apical branches, with bilateral pleural effusion moderate on the right and minimal on the left, a cardiomegaly and an apical thrombus in the left ventricle. The abdominal sections show the presence of foci of renal and hepatic infarction Figure 2.

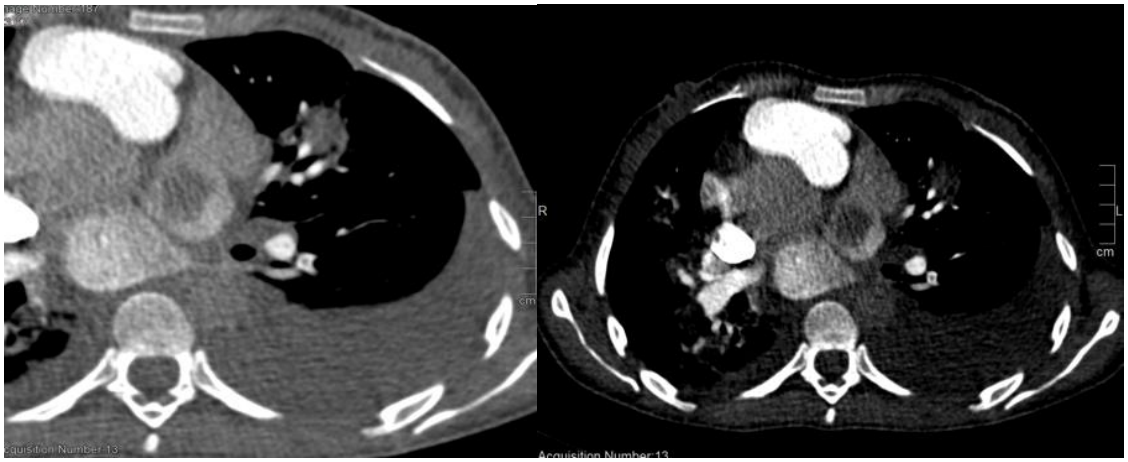

Fig-1: Computed tomography pulmonary angiography shows pulmonary embolism

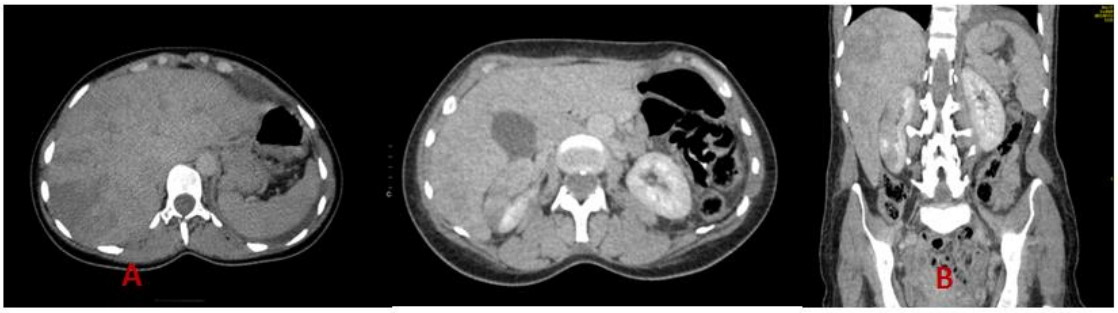

Fig-2: Computed tomography abdominal angiography A: transversal sections shows the presence of foci of hepatic infarction, B: Coronal section shows the presence of foci of right reanal infarction

Before initiating anticoagulant treatment, the main coagulation parameters of the patient were: erythrocytes 4.27 106/ L, hemoglobin 11.5 g/dL, hematocrit 40%, platelet 259.103/ L and D-dimers were positive, INR1.19, renal and hepatic assessments were normal.

The routinely performed transthoracic echocardiography revealed an enlarged left ventricle with severely reduced ejection fraction (EF: 20%, calculated by Simpson's method) due to global hypokinesia and mobile and echogenic mass (apical thrombus) Figure 3 measured 35x19 mm. The right cavities were dilated with severe right ventricle dysfunction (FR=29%, TAPSE at 14mm and S'RV at 7cm/s) and pulmonary arterial pressure was estimated at 30 mmHg, associated to moderate aortic and mitral regurgitation.

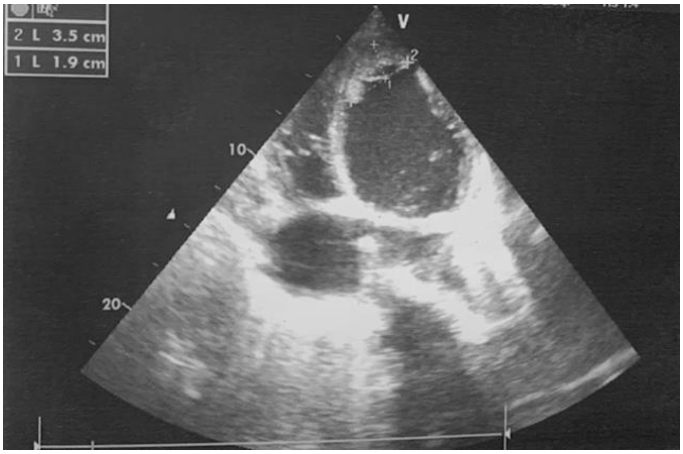

Fig-3: Transthoracic echocardiography, four chambers view: Apical left ventricular thrombus

To find out the source of thromboembolic events and as primary screening for malignancies, venous and abdominal ultrasound examinations were performed. Venous duplex Doppler examination of the lower limbs excluded the presence of deep vein thrombosis.

Embolic or ischemic etiology was not ruled out by angiography; however, the patient had no history of angina or myocardial infarction, and there were no regional wall motion abnormalities on transthoracic echocardiography suggesting coronary disease. We considered the cardiomyopathy as having non-ischemic etiology, as well as a thrombophilia assessment was carried out confirming the factor V Leiden mutation.

During the hospital stay, the patient developed a transient alteration of neurological status with dysarthria and signs of central facial paralysis. Angio-MRI objectified an ischemic stroke at the acute stage of the deep territory of the right anterior cerebral artery (figure 4).

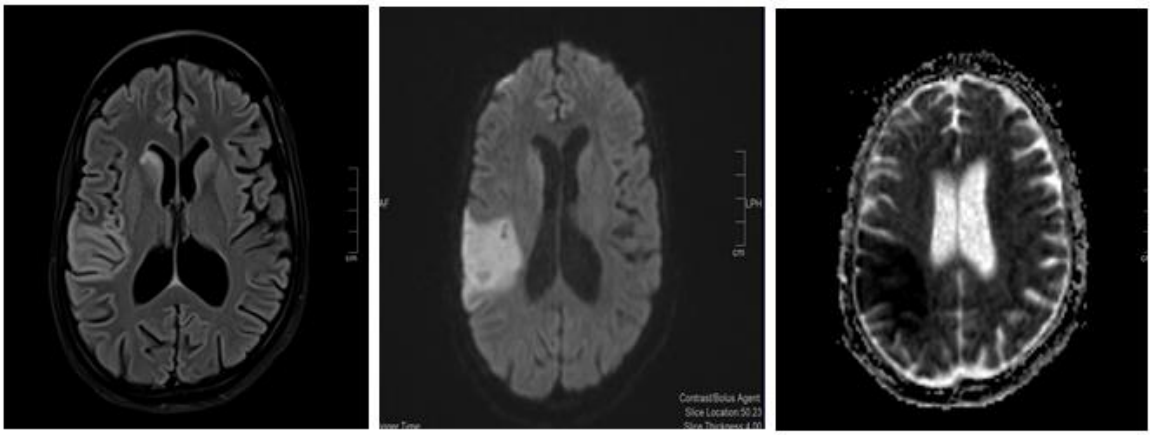

Fig-4: Magnetic resonance imagery angiography, transversal sections shows ischemic stroke at the acute stage of the deep territory of the right anterior cerebral artery

Therapeutic anticoagulation was started with enoxaparin since we objectivated the pulmonary embolism, and continued later with rivaroxaban. Since our patient was hemodynamically stable, there was no indication for systemic thrombolysis.

DISCUSSION

Among the congenital disorders of hemostasis, familial thrombophilia due to a factor V mutation, known as factor V Leiden (named after the town where the anomaly was discovered), is of particular importance because of its high frequency in the population and the serious thrombotic complications it is likely to generate [1].

In addition, Factor V Leiden can no longer act as a cofactor for activated protein C (in the presence of phospholipids, calcium and protein S). This results in the persistence in the circulation of activated factor V, which cannot be cleaved by activated protein C, and thus a tendency to hypercoagulability, protein C being one of the many physiological anticoagulant systems through its inhibitory effect on factor V [2].

It is an autosomal dominant inheritance, usually revealed by superficial or deep venous thrombosis, much more rarely by pulmonary embolism, sometimes with a particular localization such as cerebral, mesenteric or portal venous thrombosis, of a spontaneous and recurrent nature, occurring in subjects under 45 years of age, most often heterozygous, the thrombogenic risk being ten times higher in homozygous subjects [1].

Few arterial accidents due to factor V Leiden were reported until 1999, and several studies have failed to demonstrate a significant difference in the prevalence of factor V mutation in myocardial infarction or stroke [3]. Thus, a first study in 1995, involving a large series of patients with factor V Leiden, did not find an increased risk of myocardial infarction [4], the relationship with arterial risk did not appear to be clear, which was corroborated by two other studies dating from 1998 [5]. There is therefore no significant prevalence of familial thrombophilia in young patients with unexplained myocardial necrosis, without coronary atheroma [6]. However, in 1997, authors pointed out that factor V Leiden could be associated with the early occurrence of unexplained arterial thrombosis in the cerebral and coronary networks in particular [7].

Specific localizations are described with several cases of small bowel infarction, including two cases on arterial occlusion [8], as well as a case of

mesenteric thrombosis where the factor V mutation was identified by PCR [9]. The risk of arterial thrombosis without stenosis seems to be most often related to a deficiency of protein C, antithrombin III and especially protein S, or to a gene mutation of factor II, especially in young women, but several factors are most often associated in the determination of hereditary thrombophilia with clinical expression [10, 11].

The mutation may be asymptomatic, but the risk of developing a thrombotic event compared with the general population is increased sevenfold for heterozygotes and eighteenfold for homozygotes [12]. This risk is increased by age and by the use of oral contraceptives and pregnancy in women. The factor V mutation may be associated with other pro-thrombogenic abnormalities such as protein C and S deficiency, antithrombin III deficiency, homocysteinemia and the presence of antiphospholipid antibodies [13], other authors have found an association with a positive rheumatoid factor [14].

Testing for the FV Leiden mutation by PCR (diagnosis of certainty) is indicated, possibly after a phenotypic screening test (resistance to the anticoagulant action of activated protein C, RPCA) made specific for FV by dilution of the plasma with FV-deficient plasma, in the following situations [15]:

1. A subject under 60 years of age who has had a first spontaneous venous thromboembolic episode (proximal deep vein thrombosis and/or pulmonary embolism),
2. A woman of childbearing age, whether the episode is spontaneous or induced.
3. Recurrence of proximal DVT and/or PE, provoked or not.
4. After a first episode before the age of 60 and in case of recurrence of unprovoked distal DVT who's first episode occurred before the age of 60.

In the context of family studies, this research may be carried out in first-degree relatives in the case of homozygous FVL or heterozygous FVL-FII mutation. In the case of a diagnosis of heterozygous FVL, it is recommended that a family study be considered only in women of childbearing age and after clear information on the possible consequences (contraception, pregnancy, etc.). Apart from the higher prevalence of VTE and slightly shorter VTE-free survival, VTE penetrance and phenotype severity were not significantly different in homozygous or heterozygous carriers, suggesting that VTE prevention and management should not differ according to Factor V Leiden genotype [13].

In addition, numerous associations of factor V Leiden with other congenital defects have been described, including the G 20210A mutation in the prothrombin gene. In all cases, the thrombotic risk is higher in patients with combined deficiencies.

Once the diagnosis of factor V Leiden mutation has been made, the family should be investigated in order to quickly identify other subjects also affected by this familial thrombophilia, and to broaden the etiological work-up to look for other associated anomalies. As the venous thromboembolic risk is well known, prevention begins with good knowledge and information about risk situations and the therapies that should be discussed (oral contraception, hormone replacement therapy). The recurrence of a venous thrombosis leads to a case-by-case discussion of the introduction of anticoagulant treatment [15].

It was difficult to select appropriate coagulation therapy for those patients. Warfarin therapy is recommended for LV thrombosis after myocardial infarction rather than surgical removal according to both the European Society of Cardiology and the American Heart Association guidelines [16]. Recently, Nagamoto *et al*. reported resolution of an LV thrombus resulting from previous myocardial infarction 27 days after dabigatran initiation [17]. Chung *et al*. also reported resolution of an LV thrombus with acute ischemic stroke and atrial fibrillation 7 days after dabigatran initiation [18]. Nakasuka *et al*. reported resolution of an LV thrombus secondary to tachycardia-induced heart failure 7 days after rivaroxaban initiation [18]. Further studies are needed to confirm the efficacy of Novel oral anticoagulants (NOAC) for treating left ventricular thrombosis.

Testing for the FVL mutation before prescribing estrogen-progestif oral contraception in a young girl, or before pregnancy, if a heterozygous FVL mutation is detected in the index case, is debatable and should be considered on a case-by-case basis.

CONCLUSION

The factor V Leiden mutation is the genetic polymorphism most frequently implicated as a predisposing factor for venous thrombosis. It is responsible for a prothrombotic state due to a slight imbalance between the coagulation and anticoagulation processes. It is often associated with venous occlusions; arterial involvement is related to the absence of recirculation after the occurrence of thrombosis and is responsible for complicated forms of neovascularization.

Conflicts of interest

There are no conflicts of interest.

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