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Hereditary thrombophilia by factor V Leiden G1691A (heterozygous) and FII prothrombin G20210A (homozygous) mutations in a patient with ischemic cerebrovascular accident

Trombofilia hereditária por mutações G1691A do fator V Leiden (heterozigota) e G20210A do FII protrombina (homozigota) em paciente com acidente vascular cerebral isquêmico

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ABSTRACT

Mutations related to Factor V Leiden (G1691A) and prothrombin (G20210A) are associated with a significantly increased risk of venous thromboembolism. The identification of a patient affected by episodes of venous thromboembolism and carrier of G1691A (heterozygous) and G20210A (homozygous) polymorphisms was determined by molecular tests [real-time polymerase chain reaction (PCR) methodology, Genexpert system] during attendance at the Base Hospital of São José do Rio Preto-SP, Brazil.

Key words: thrombophilia; mutation; venous thrombosis.

INTRODUCTION

Venous thromboembolism (VTE) is a disease in which intrinsic factors and several acquired factors may be involved, so that deep venous thrombosis (DVT) and pulmonary thromboembolism (PTE) are the main causes of death[1]. Deficiencies of coagulation factors, platelet abnormalities, blood vessel wall abnormalities, and changes of coagulation inhibitors may contribute to the development of thrombosis. Factor V Leiden (FVL) and factor II prothrombin G20210A gene mutation are among the major risk factors for thromboembolism[2].

FVL is the most common genetic risk factor for VTE, found in 20%-25% of VTE patients and in 50% of hereditary thrombophilia[3]. This genetic disorder is characterized by poor response to activated protein C (APC). APC is a natural anticoagulant protein that cleaves and inactivates procoagulant factors Va and VIIIa, thereby decreasing the formation of thrombin[4]. FVL arises from the specific replacement of guanine by adenine at nucleotide 1691 in the gene for factor V, determining the replacement of glutamine by arginine at the APC-cleavage site. As a result of this single amino acid substitution, factor Va becomes resistant to APC, and its inactivation is ten times lower than normal. Cleaved FV also works as a cofactor for APC-mediated inactivation of factor VIIIa. Thus, an increase in thrombin generation occurs[5].

Prothrombin or factor II (FII) is a protein (zymogenic) vitamin K-dependent, produced by the liver, and plays a central role in the conversion of fibrinogen to fibrin. Molecular analyzes in the prothrombin gene revealed guanine replacement by adenine at position 20210, which is related to the increase in the number of cases of DVT recurrence[6]. The FII G20210A polymorphism is associated with increased plasma prothrombin levels, and its carriers present a 2-3 fold increased risk for the development of venous thromboembolism[7].

CASE DESCRIPTION

Female patient, 43 years old. The patients presented previous history of five ischemic cerebrovascular accidents (iCVA), the first at 36 years of age, with probable cardioembolic cause, taking Marevan

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since the first episode, discontinued medication in December 2016 and began acetylsalicylic acid administration. She was admitted to hospital in the end of February 2017 due to dyspnea, with extensive bilateral PTE with areas of pulmonary infarction (**Figures 1** and **2**). At the hematology service care, on April 24, 2017, she restarted the treatment with Marevan with increased dosage (5 mg, ½ tablet on Saturdays and one tablet on the other days of the week), and heparin (5000 UI, subcutaneous, 12/12 hours).

Due to the clinical condition of the patient, researches were ordered to determine thrombophilia, including the investigations for FVL and FII prothrombin mutations, scheduled to return on May 08 to International Normalized Ratio (INR) evaluation.

The molecular exams results revealed polymorphisms associated with FVL, G1691A heterozygous mutant, and prothrombin FII, G20210A homozygous mutant (**Figure 3**).

On the return on May 2017, the patient was asymptomatic and INR within the normal range. The dosage of Marevan was maintained, heparin was discontinued and genetic counseling (letter sent) was performed on the possibility of their children being heterozygous carriers of the detected mutations. The patient was informed on the need for prophylaxis with heparin in case of exposure to risk factors (surgeries, pregnancy, puerperium, immobilizations, etc.).

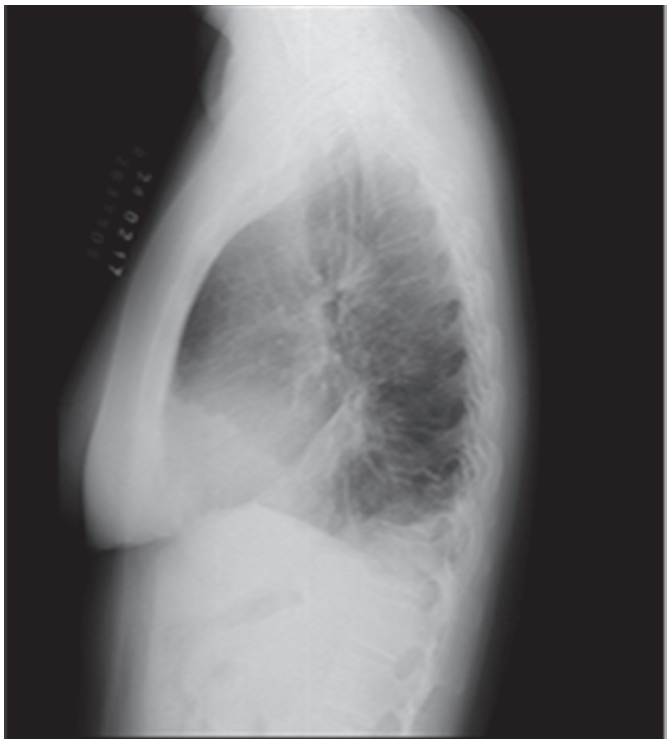

FIGURE 1 – *Lateral chest X-ray. Opacity in right lung base and in midfields and left lung base, due to air space filling lesions*

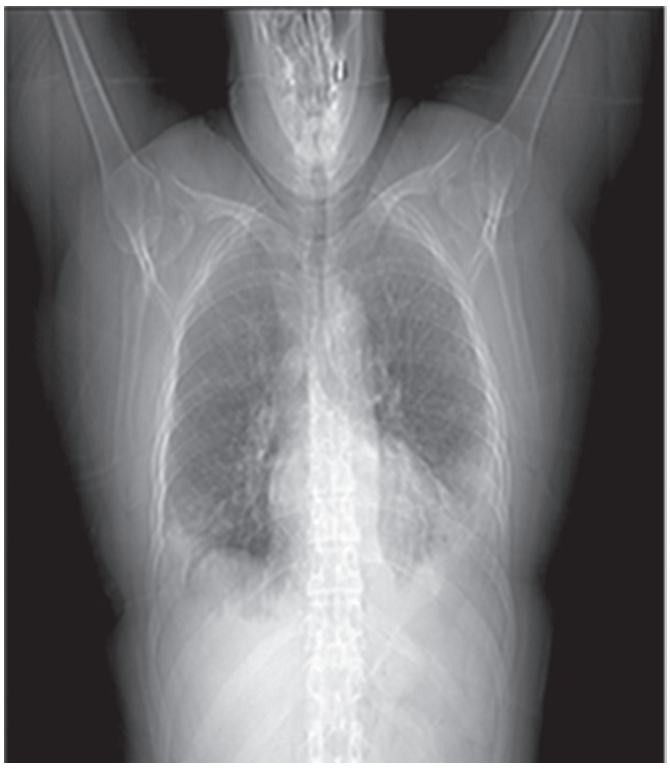

FIGURE 2 – *Chest CT scan. Pulmonary artery filling defect in the right and left branches. Possible pulmonary infarction in the right and left lower lobe*

CT: computed tomography.

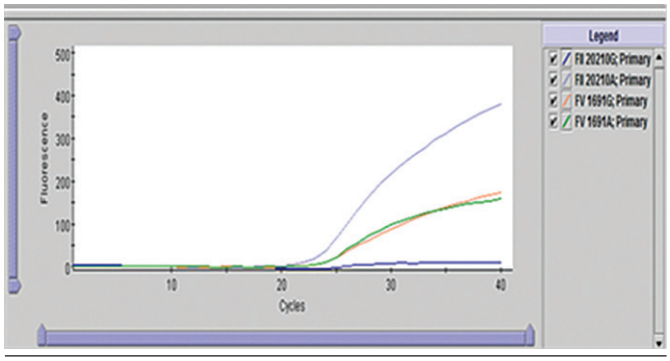

FIGURE 3 – *Real-time PCR, GeneXpert system. Amplification of the gene G20210A mutation (purple curve) and genes G1691A mutation (green curve) and wild-type G1691G (orange curve)*

PCR: polymerase chain reaction.

DISCUSSION

The risk of thromboembolism is greater in patients with homozygous mutations or in patients carrying double heterozygosity. Heterozygous carriers of FVL who had an episode of VTE present, on average, a 40% increase in the risk of recurrent episodes when compared with non-carriers patients. The risk is

lower for heterozygous FII prothrombin. The decision to extend the recommended anticoagulant therapy period in patients with polymorphisms remains individual, depending on a number of factors, including associated comorbidities[8].

Our study presents the identification of a homozygous G20210A, heterozygous FVL G1691A patient, which was affected with VTE episodes (iCVA and PTE). FII G20210A occurs in approximately half of patients with factor V polymorphisms and is present in 6% of patients with a family history of VTE[6]. The prevalence of FII G20210A polymorphisms was determined for patients who had non-traditional risk factors for thromboembolism (diabetes, hypertension and hyperlipidemia) and those affected by episodes of cerebral ischemia, with a rate of 9.7% heterozygotes and 2.8% homozygotes[9]. The homozygous G20210A mutation carriers described in the literature are rare. Seventy cases were reported, showing high phenotypic diversity[10]. Poort *et al.* (1996)[6] described the diagnosis of a woman from a family with 24 cases of thrombotic symptoms, as a homozygous G20210A carrier and heterozygous for FVL G1691A.

A global systematic review of the published literature on G20210A polymorphisms, including 113 articles from the six continents (Africa, Asia, Oceania, Europe, North America and South America) and 67 countries, identified symptomatic G20210A homozygote (VTE) in Poland (0.2%), Jordan (0.2%), gypsies from Slovakia (0.6%) and in northeastern Greece (0.6%). No case of homozygous G20210A carriers has been reported in South America. Symptomatic heterozygous carriers (VTE) ranged from 1% for Africans to 10.4% in the Caucasian population[11].

RESUMO

Mutações relacionadas com o fator V de Leiden (G1691A) e a protrombina (G20210A) estão associadas a um significativo aumento do risco de tromboembolismo venoso. Por meio da realização de exames moleculares [metodologia de reação em cadeia da polimerase (PCR) em tempo real, sistema Genexpert], em pacientes atendidos no Hospital de Base de São José do Rio Preto-SP, Brasil, foi determinada a identificação de uma paciente afetada por episódios de tromboembolismo venoso e portadora dos polimorfismos G1691A (heterozigota) e G20210A (homozigota).

Unitermos: *trombofilia; mutação; trombose venosa.*

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