Resistance to Activated Protein C and Ischemic Arterial Disease in a Young Man

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The assessment of activated protein C resistance (APCR) caused by mutations in factor V (factor V Leiden) is an important risk factor for venous thromboembolism, of which role as the originator of arterial obstructions in situ is still a controversial subject. The clinical case of a young patient with history of coronariopathy, multiple cerebrovascular lesions and peripheral artery disease is reported. The diagnostic investigation showed APCR as the possible etiology.

Introduction

Thrombophilias can be described as inherited or acquired defects of homeostasis that cause hypercoagulability. Among the most often cited are the anticardiolipin antibody, lupus anticoagulant, proteins C and S deficiencies, factor V Leiden (FVL) and the G20210A mutation of the prothrombin gene.

The FVL comes from the factor V mutation, which leads to activated protein C resistance (APCR) and the consequent higher formation of thrombin[1]. It is considered one of the most common abnormalities of the coagulation system, with a prevalence of 3%-5% among the Caucasian population[2]. Its detection is ideally achieved through polymerase chain reaction (PCR) and restriction fragment polymorphism analysis (RFLP). It can also be assessed by a coagulometric method, more easily available clinically and that presents excellent sensitivity and specificity when compared to the PCR technique[3].

Several studies have demonstrated the association between APCR and venous embolism. However, its association with ischemic arterial events is quite controversial, even though many researchers have been studying the subject for more than 10 years[1].

The objective of the present study is to report the clinical case of a patient with multiple ischemic arterial events (coronariopathy, cerebrovascular disease and peripheral artery disease), without traditional risk factors and with APCR.

Key Words

Thrombophilia; factor V; blood coagulation; protein C resistance; arterial occlusive diseases.

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Case report

A 38-year-old male, Brazilian mixed race, married patient, who worked as a private security guard, originally from the town of Iguatu, state of Ceara, Brazil, and a resident in the city of Curitiba, state of Parana, Brazil, suddenly presented in 1999, at 29 years of age, speech difficulties, dropping of the left side of the body, dizziness and disorientation. He was treated as presenting a cryptogenic vascular encephalic accident, with total neurological recovery. In 2005, he underwent a head tomography, which showed hypodense areas in the cerebellum, occipital lobe, internal capsule and thalamic region, suggesting ischemias at these levels (Figure 1).

The patient remained asymptomatic until April 2007, when he presented intense retrosternal chest pain and burning sensation. A coronary angiography was carried out, which disclosed a critical lesion in the first diagonal branch of the anterior descending artery and the patient was submitted to stent implantation. In November 2007, the patient underwent a transesophageal echocardiography, which revealed mitral and tricuspid valve prolapse with minimum reflux, left ventricular relaxation and normal internal dimension, segmental and global contractility. A perfusion echocardiography with microbubbles was performed. When preparing the contrast, 9 mL of distilled water was added to 1 mL of ambient air in a syringe, of which content, after being agitated, was injected into the venous access. The test was considered negative, as there were no microbubbles in either the right or left atria after three cardiac cycles post-injection.

In August 2008, a pulse asymmetry was detected in the upper and lower limbs and the patient was then admitted at the Hospital de Clínicas of the Federal University of Parana. He reported systemic arterial hypertension and dyslipidemia diagnosed 4 months before controlled with captopril and simvastatin, respectively. The patient also used ASA and propranolol.

The patient denied similar cases in the family or other familial diseases, smoking or illicit drug use. He presented good general state, BMI of 24, blood pressure of 110/60 mmHg and heart rate of 72 bpm. The precordium assessment was normal. He presented decreased brachial pulse amplitude and absence of radial and pedis pulse to the left. The capillary filling was slow in the left hand and foot.

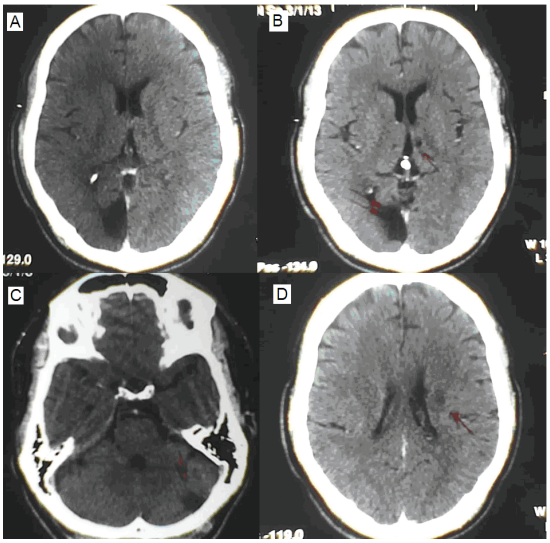

Figure 1 - Head ACT showing ischemic lesions (A) in the right occipital region; (B) right occipital and left thalamic; (C) left cerebellar region and (D) in the region of the left internal capsule.

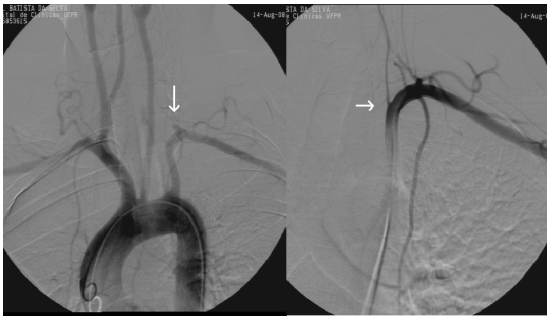

Figure 2 - Arteriography of the aorta and base vessels. The arrows indicate critical stenosis of the left vertebral artery.

The neurological assessment showed nasal campimetric alterations in the right eye and temporal alterations in the left eye.

Complete blood count, electrolyte, creatinine and liver enzyme measurements were performed and were within the normal range. Total cholesterol, HDL-c, LDL-c and triglycerides were, respectively, 143, 38, 83 and 109 mg/dL. During hospitalization, a brain arteriography was performed and disclosed a critical stenosis of left vertebral artery (Figure 2). The vascular US showed a slight hypoflow in the subclavian, brachial and ulnar arteries to the left and absence of flow in the mid and distal thirds of the left anterior tibial and radial arteries, suggestive of occlusion.

Lupus anticoagulant, antithrombin III, anticardiolipin, cryoglobulins, fibrinogen measurement, protein C, protein S, homocysteine and falcization tests were performed and al results were negative or within the normal range, without exception. The APCR was tested with a functional coagulometric assay (*Coatest APC Resistance*, Diapharma, U.S.A.), with a dilution in FV-deficient plasma and was considered positive. The observed result was > 120 seconds. The patient was discharged on long-term anticoagulation with warfarin.

Discussion

The presence of FVL and, consequently, APCR, significantly increases the risk of venous thrombotic events. Such impact was first demonstrated by the Leiden Thrombophilia Study, which showed an almost 7-fold higher risk of venous thrombosis. The confirmation was given by another prospective study with 14.916 patients, which observed a 2.7-fold relative risk for venous thromboses[1].

As in other types of thrombophilias, the APCR triggers venous-obstructive conditions concomitant to clinical pictures such as postoperative periods, trauma, pregnancy/postpartum or burn wounds[1,2]. Smoking and oral contraceptives have also shown to be important adjuvant factors. No triggering factor or clinical picture was identified in the case of the patient reported here.

After the publication of two cases of acute myocardial infarction (AMI) in young patients who were homozygous for FVL and other cases related to cerebrovascular disease[1], several investigators suggested an association with arterial thrombotic events.

An experimental study demonstrated that animals that were homozygous and heterozygous for FVL presented a significant increase in carotid thrombosis after physical-chemical injury[4]. Gluek et al[5], in a case-control study, suggested an association between thrombophilia and arterial thromboembolic events, with a higher prevalence among men. Van de Water et al[6] found a higher prevalence of FVL in infarcted patients, younger than 50 years and with normal or almost normal coronaries, when compared to patients that presented severe coronary stenosis.

It is also suggested that the APCR, in concomitance with situations such as hyperhomocysteinemia[7] or diabetes[8] can be a risk factor for brain ischemia[1]. Moreover, cases of ischemic peripheral artery disease have been reported in patients with FVL.

However, large studies such as the Copenhagen City Heart Study[1], did not show an association between APCR and AMI or cerebrovascular disease. Similarly, Ercan et al[9] did not find an association between AMI and FVL, when evaluating a population with a higher prevalence of classic risk factors for atherosclerosis.

Finally, a recent prospective study that followed 542 patients for 11 years showed no association between the presence of FVL and increased risk of recurrent cardiovascular events after AMI[10].

The lack of definitive data on the association between FVL-APCR as the etiology of ischemic arterial disease *in situ* impairs the development of studies on the natural course of the disease and the search for effective treatments. Regarding the venous thrombosis, the benefit of the anticoagulation with

coumarins has been demonstrated, with an approximate risk reduction of 90%[11]. The treatment of asymptomatic patients is not indicated.

In the case reported here, the long-term anticoagulation with warfarin was the chosen treatment. However, it is worth mentioning the importance of individualized therapeutic management, evaluating the benefits and known risks of oral anticoagulation.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

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