We describe the clinical case of two siblings with different presentations of thrombotic phenomena, in which prothrombin mutation was observed.

Thrombophilia may be due to the presence of one or more genetic factors, or chronic diseases such as morbid obesity, cancer, inflammatory bowel diseases, or the persistence of antiphospholipid antibodies or even transient conditions that temporally predispose to clot formation, such as recent surgery, trauma, prolonged bed rest, pregnancy, the use of oral contraceptives or hormone replacement therapy.

The most common causes of inherited thrombophilia are: prothrombin 20210A mutation, factor V Leiden mutation, protein C deficiency, protein S deficiency, antithrombin III deficiency and hyperhomocysteinemia.

Case Reports

Case 1 - A 28-year-old female patient admitted because of prolonged thoracic pain with nausea and dyspnea. She smoked 20 cigarettes/day and led a sedentary lifestyle. Her medical history was otherwise unremarkable.

On physical examination, blood pressure was 120/80 mmHg and heart rate was 80 bpm. Cardiac auscultation revealed a regular rate rhythm with a S4. The remainder of physical examination was normal.

The ECG showed ST-segment elevation in leads V1 to V3. Echocardiogram showed anterior-apical hypokinesia. The patient underwent cardiac catheterization four days after the pain episode, and the exam indicated the presence of thrombi in the anterior descending coronary artery with slow flow in this artery, suggesting that there had been spontaneous recanalization.

The cause of her thrombophilia was investigated. PT, APPT, anticardiolipin antibodies, protein C, protein S, antithrombin III, ANF and VDRL tests were performed, and no alterations were detected. Test for prothrombin mutation was positive in heterozygous pattern. At the time of the follow-up visit after hospital discharge, the patient was asymptomatic and receiving aspirin, atorvastatin and ramipril. The electrocardiogram revealed Q wave from V1 to V3, and the control echocardiogram showed antero-septal akinesia.

Case 2 - A 30-year-old male patient presented with complaints of tachycardia and dizziness for three days. He had no antecedents of cardiovascular diseases.

Physical examination was normal except for the irregular cardiac rhythm. ECG indicated atrial fibrillation and heart rate of 120.

Laboratory tests were normal. Transthoracic echocardiogram was normal (measurement of the left atrium was 3.2 cm), but transesophageal echo showed a thrombus in the left atrium.

Test for thrombophilia was negative except for prothrombin mutation.

Upon discharge, the patient was taking warfarin and was instructed to keep INR at about 2.0. At the follow-up visit, patient was asymptomatic, with no new episodes of atrial fibrillation.

Discussion

Prothrombin 20210A mutation, also called factor II mutation, is a change in the genetic code that leads to increased prothrombin production. This condition was first described in 1996 and is found in 2% of the caucasian population in the USA. Most carriers of this disease are heterozygous for this genetic mutation. Prothrombin mutation occurs with equal frequency in both sexes. Its presence is associated with a 2-3-fold increased risk of developing deep venous thrombosis. Women with prothrombin mutation and using oral contraceptives are at a 16-fold increased risk of developing deep venous thrombosis. It also seems that prothrombin mutation affects more frequently women who had complication during pregnancy (fetal loss after the 20th week, premature placenta separation and preeclampsia).

The relationship between atherosclerosis and thrombosis has been recognized a long time ago, but only recently it was understood that certain hemostatic factors affect not only thrombus formation, but have also a direct atherogenic effect. Atherosclerosis is a complex disorder that results from the interaction of multiple genetic and environmental factors. Several polymorphisms and mutations in genes related to the...
hemostatic system, and to vascular determinants that modulate the bioavailability of nitric oxide, have been identified in the last decade.

When one reads about “coronary artery disease instability”, the concept of “vulnerable plaque” comes to mind. Some authors propose that we also pay attention to “vulnerable blood”, as that prone to thrombosis. Some platelet polymorphisms such as GI IIa, Ib-alfa gene 5T/C Kozak sequence, factor V and factor VII have been reported as independent risk factors for myocardial infarction.

Acute myocardial infarction is a complex, polygenic, multifactorial condition that results from the interaction between the genetic patrimony and many environmental factors. Although each risk factor for coronary disease is partially controlled by genetics, familial history of coronary heart disease is also an important predictor, suggesting the presence of additional genetic susceptibility for this condition.

Some patients who suffered an acute myocardial infarction did not have any of the traditional cardiovascular risk factors, supporting the role of a genetic component that has not been characterized. Genetic linkage studies and candidate gene analysis have identified a locus and several candidate genes in the predisposition to acute myocardial infarction.

Dropinski related the case of a 32-year-old man who had suffered two episodes of myocardial infarction without having any of the classic risk factors for atherosclerosis. Laboratory tests disclosed primary antiphospholipid syndrome, Leiden factor V mutation and mild hyperhomocysteinemia that may be predisposing factors for coronary occlusion.

However, studies suggesting that mutation in specific coagulation genes may act as a genetic basis for cardiovascular risk are, sometimes, contradictory. Wu reviewed clinical studies that examined the role of nucleotide polymorphism in coagulation factors and in platelet activity to determine if specific genotypes are correlated with history of thrombotic arterial events (acute coronary syndrome or stroke). A meta-analysis of factor II, Leiden factor V, factor VII and GPIIIa studies was performed, and no correlation between polymorphism of factor II or factor V and coronary heart disease was found. Correlation was found between factor V and CVA, as well as between GP II and coronary artery disease.

It has been observed that certain cardiac arrhythmias may change plasma levels of hemostatic markers, depending on the left atrial appendage function. Sakurai conducted a study comparing three groups of patients: one group with atrial fibrillation, the second one with atrial flutter and the third with sinus rhythm. Plasma levels of platelet activity markers were evaluated (platelet factor IV and beta-thromboglobulin), thrombotic state (complex thrombin-AT III and fragments 1 and 2 of prothrombin) and fibrinolytic state (d-dimer and plasmin-alfa-2-plasmin inhibitor complex) were evaluated.

No difference was found in the plasma levels of hemostatic markers between the atrial flutter group and the sinus rhythm group. However, patients with atrial flutter and altered left atrial appendage function had greater levels of d-dimer and beta-thromboglobulin than patients with normal left atrial appendage function.

In the first case of this report, the patient had some classic risk factors for coronary disease, such as cigarette smoking and sedentarism. But these were just two among the ten traditional risk factors. Therefore, it is very likely that the prothrombin mutation was responsible for coronary occlusion. In the second case, atrial fibrillation alone is, in itself, considered a risk factor for clot formation. However, prothrombin mutation may also be considered an additional risk factor for the clot formation in this patient.

The lesson to be learned from these cases is that young patients who experience myocardial infarction, as well as their relatives, should be tested for thrombophilia.

References