Case Report

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A Cryptogenic Stroke Associated with Non-Infectious Endocarditis and Pai Mutation- Case Report

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ABSTRACT

Ischemic stroke is the most common neurological complication of endocarditis. Approximately 20% of patients with infective endocarditis (IE) present with stroke and in more than a third of them with nonbacterial thrombotic endocarditis (NBTE). Stroke is often one of the first symptoms of endocarditis. Population-based studies on cryptogenic stroke as defined by TOAST is 25% [1]. Not only the acquired risk factors are significant in vascular incidents, but also the genetic. The predisposition to thrombosis may be a result of genetic factors, acquired changes in the clotting mechanism or interaction between them. Impaired fibrinolytic function secondary to elevated plasminogen activator inhibitor-1 (PAI-1) levels has been implicated in ischemic stroke. We present a clinical case of a 33year old female with several ischemic strokes with unknown cause.

Keywords: Thrombophilia; Non- Infectious Endocarditis; Stroke

Introduction

Stroke in young adults is associated with significant morbidity, and mortality. The mechanisms causing stroke in young adults are unique and could be associated with thrombophilia, autoimmune disease. In this article we emphasize the need of excluding genetic predisposition for thrombotic events as well as autoimmune disease as an inflammatory vessel damage. Diagnosing young adults with attacks of acute neurological deficit could be challenging and testing for thrombophilia should be considered. Thrombophilia is defined as a predisposition for abnormal clot formation. It is a polygenic disorder with variable expressivity. A predisposition to thrombosis may be a result of genetic factors, acquired changes in the clotting mechanism, or more commonly, an interaction between them. Homozygous carrier or the combination of two or more heterozygous abnormal factors can lead to thrombotic disorders in young adults under 45 years.

Materials and Methods

Somatic and neurological examination, laboratory tests, computed tomography (CT), doppler ultrasound examination, echocardiography and trans esophageal echocardiography.

Clinical Case

We present a clinical case of a 33year old female admitted to the hospital with complaints of numbness and weakness in right limbs and speech disturbances. Neurological examination showed right severe hemiparesis and motor aphasia. The patient has history for ischemic strokes in the vessel territory of the right and left middle cerebral artery with fully recovery. No risk factors for thrombotic events were found prior to hospitalization. CT of the brain revealed chronic ischemic lesions in the left, fronto-parieto-temporal area and right caudate nucleus. (Images 1 & 2). Duplex doppler sonography of the brain vessels did not found any pathological changes. The patient was tested for thrombophilia (factor V Leiden, prothrombin mutation G20210A, MTHFR C677T and A1298C mutation, PAI mutation 4G/5G). Homozygous caring for PAI 4G/4G mutation was found. The patient was consulted with cardiologist for seeking for additional risk factors. Continuous holter-ECG was performed, arrhythmia was excluded.

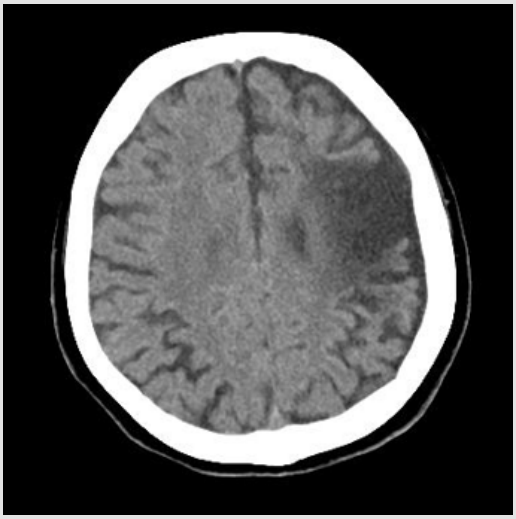

Image 1.

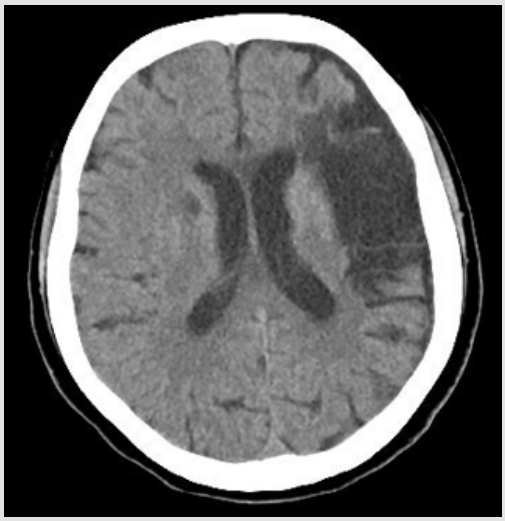

Image 2.

The patient was tested additionally with transesophageal echocardiogram (TEE). It showed no evidence of thrombosis in the left atrium. Aortic valve was with no pathological structures or changes. On the mitral valve were found several small vegetations on both leaflets, relatively soft with a size of 5/5 mm, with an irregular shape, and for the subvalvular larger formation also relatively soft with dimensions of 15/10 mm, directly related to the available vegetation. Mitral valve formations were categorically thrombogenic. Persistent foramen ovale was not found also after intravenous saline contrast administration. Several sets of blood cultures were taken despite the presence of normal values for C-reactive protein and procalcitonin. Non-bacterial (Libmann Sacks) endocarditis was suspected because the missing history for fever episodes and negative results for bacterial growth from the blood cultures.

Libmann Sacks endocarditis was observed. The patient was tested for antiphospholipid and antinuclear antibodies. The results were negative. A CT of the abdomen and chest was done to exclude malignancy. A CT scan showed evidence of stenosis/agenesis of the infrarenal section of the inferior vena cava (Image 3). Because of the absence of correctable disease (tumor, autoimmune disorder), surgery treatment was discussed. The mitral valve was changed with mitral-valve prosthesis with a biological valve prosthesis: MVR SJM Epic No29/ tissue valve/. She was discharged with vitamin K anticoagulant treatment.

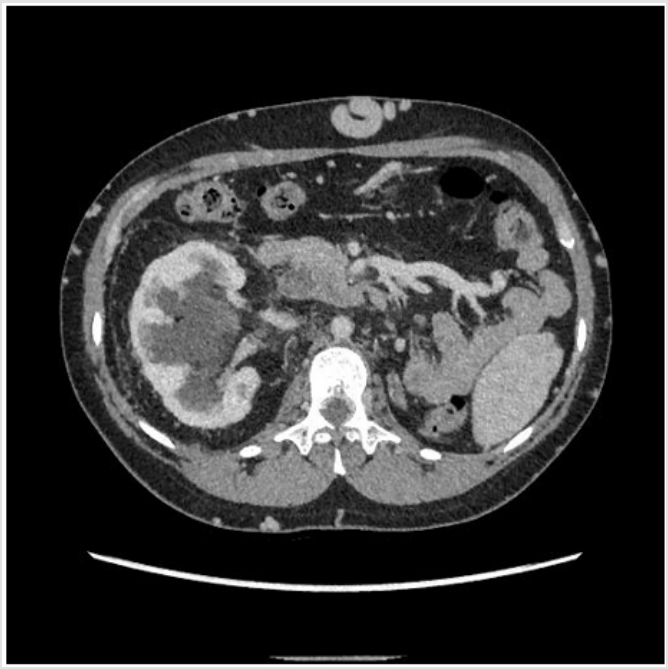

Image 3.

Discussion

Homozygous carrying of the PAI mutation, 4G/4G is clinically significant for thrombotic events. Increased plasma activity of PAI-1 leads to reduced fibrinolytic activity and increased risk of arterial and venous thrombosis. Decreased fibrinolytic capacity due to increased plasma levels of PAI-1 plays an important role in the pathogenesis of thrombotic events [2]. Individuals who are homozygous for the 4G allele have increased plasma PAI-1 concentrations compared to those with the 5G allele [3]. In some studies, the prevalence of the 4G allele has been found to be higher in coronary artery disease, meningococcal septic shock, osteonecrosis, severe preeclampsia, pulmonary thromboembolism (PTE) [4-6]. Libman-Sacks endocarditis, also known as verrucous endocarditis, is a form of nonbacterial thrombotic endocarditis (NBTE). It is characterized by presence of sterile vegetations on the valves. These sterile vegetations may be associated with malignancy, autoimmune disease like systemic lupus erythematosus, or antiphospholipid antibody syndrome and are more frequently found on mitral and aortic valves. More studies were needed to understand the pathophysiology of NBTE. In most of the cases an endothelial injury from circulating cytokines such as TNF (tumor necrosis factor) or interleukins in a hypercoagulable state patient causes platelets aggregation and inflammatory molecules in the affected valves. The vegetations consist mainly of immune complexes, mononuclear cells, fibrin, and platelets. These vegetations are small (<10mm), may sometimes be larger (>10mm) [7-9].

Libman-Sacks endocarditis should be discussed in young patients with ischemic stroke. It is mandatory to check them for underlying malignancy, systemic lupus erythematosus, and antiphospholipid antibody syndrome. Blood cultures are necessary to rule out other etiologies such as infective endocarditis. Trans-esophageal echocardiography has greater sensitivity and specificity than trans-thoracic echocardiography to evaluate young adults with thrombotic events. First line treatment should be focused on the underlying disease. Anticoagulation should be started as secondary prevention for thrombotic events. Prognosis is poor as patients usually have recurrent thromboembolic events and surgical treatment should be considered. Thrombotic complications in cancer can vary from arterial or venous thromboembolism to disseminated intravascular coagulation [10,11]. Despite the well-known association between cancer and thromboembolic disease, the mechanisms that promote thromboembolic events in cancer patients are not clear and appear to be multifaceted [12]. Cancer patients are generally in a hypercoagulable or prothrombotic state.

Conclusion

Ischemic stroke is severe disability disease especially for young adults. This group of patients should be evaluated not only for the prevailing risk factors. Performing tests for thrombophilia and trans-esophageal echocardiography should be part of evaluation these patients. Plasminogen activator inhibitor 1 (PAI-1) inhibits plasminogen activators and increases the risk of thrombosis. In the described case probably the homozygous caring of PAI 4G/4G mutation and increase

levels of PAI- 1 is associated with increased inflammation and greater risk for the recurrent strokes. Founding the underlying cause for thrombosis is important for the treatment. Presented case demonstrates the importance of understanding of risk factors and secondary prevention of new thrombotic events.

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