LUPINE PUBLISHERS

ISSN: 2770-5447

Advancements in Cardiology Research & Reports

DOI: 10.32474/ACRR.2023.04.000177

Review Article

Multiple Myocardial Infarctions in A Patient with MTHFR Gene Polymorphism and Sickle Cell Anemia: Case of Report

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Received: December 23, 2022 **Published:** January 10, 2023

Abstract

Introduction: Among the most important causes of mortality among individuals with sickle cell anemia are Acute Myocardial Infarction (AMI) and stroke (CVA), both related to vascular occlusion. Polymorphisms of the Methylenetetrahydrofolate Gene Reductase (MTHFR) in patients with sickle cell anemia have been considered likely risk factors for vaso-occlusive events. In this case report, we present a young patient with sickle cell anemia and C1298A polymorphism of the MTHFR gene, who suffered several episodes of acute myocardial infarction. CASE DESCRIPTION: Patient FXG, female, born on 05/23/1979, in São Paulo - SP, patient with sickle cell anemia and dyslipidemia. Patient has a history of 2 deliveries cesarean section and bilateral reduction mammaplasty. On 5/3/2016, aged 38, the patient suffers first AMI. In October 2016, the patient suffered a second episode of AMI performing angioplasty with placement of 2 stents in 2 coronary arteries. angioplasty lesion of bifurcation with stent in Anterior Descending Artery (AD) and stent in 1st Diagonal (DG1). Catheterization on 5/4/2017 showed a proximal stent in a bifurcation lesion, involving the DG1, with 80% intra-stent lesion. As for the stent originating from DG1, there was evidence of injury to 90% intra-stent. On 12/23/2017, the patient suffered a new episode of AMI. Echocardiogram transthoracic examination showed hypokinesis of the middle segment of the inferolateral and basal wall of the lower wall.

Discussion: The reported case shows the overlapping of two conditions (Sickle Cell Anemia and MTHFR Gene Polymorphism) that increase the chance of an event myocardial ischemia. It is known from the literature that genetic polymorphisms can aggravate the vaso-occlusive events of sickle cell anemia, leading to ulcer formation, priapism, stroke, avascular necrosis, infarction, and acute chest syndrome. The genetic polymorphism A1298C (Glu 429 Ala) of the MTHFR gene, as diagnosed in the presented patient, is associated with a lower activity of the enzyme Methylenetetrahydrofolate Reductase (MTHFR), responsible for catalyzing the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (active form of folic acid). This enzyme is necessary for the synthesis of purine and pyrimidine and for the restructuring of methionine from homocysteine. The decrease in the activity of this enzyme results in high levels of homocysteine (hyperhomocysteinemia), which are associated with the emergence of cardiovascular complications and possible cause of thrombotic phenomena.

Conclusion: We observe that the coexistence of sickle cell anemia and the A1298C genetic polymorphism of the MTHFR gene increased the risk of cardiovascular events and were the likely cause of repeated patient AMI episodes.

Keywords: Myocardial Infarction; Sickle Cell Anemia; Hyperhomocysteinemia; Genetic Polymorphism; Myocardial revascularization

Introduction

Among the most important causes of mortality in individuals with anemia sickle cell disease are Acute Myocardial Infarction (AMI) and Cerebrovascular Accident (CVA), both related to vascular occlusion. Polymorphisms of the Methylenetetrahydrofolate Gene

Reductase (MTHFR) in patients with sickle cell anemia have been considered likely risk factors for vaso-occlusive events [1]. The hypercoagulable state caused by sickle cell anemia may be responsible for the vascular occlusion in certain organs and by episodes of acute pain [1]. There are several causes that contribute to hypercoagulability in this disease, such as decreased levels of natural anticoagulants (e.g., proteins C and S) and increased plasma levels of homocysteine (hyperhomocysteinemia). Currently, hyperhomocysteinemia is considered a independent risk factor for coronary disease, based on the literatureRecurrent cerebral venous thrombosis associated with heterozygote methylenetetrahydrofolate reductase C677T mutation and sickle cell trait without homocysteinemia: an autopsy case report and review of literature [2]. Mutations in the MTHFR gene can compromise enzyme activity methylenetetrahydrofolate reductase, thereby decreasing folate metabolism and generating increase in plasma homocysteine [2,3]. In this case report, we present a young patient with sickle cell anemia and with C1298A polymorphism of the MTHFR gene, who suffered several episodes of acute myocardium

Case Report

Patient FXG, female, born on 05/23/1979, born and raised in São Paulo - SP, patient with sickle cell anemia and dyslipidemia. Patient has a history of 2 deliveries cesarean section and bilateral reduction mammaplasty. Your father underwent revascularization myocardial infarction at age 52. On 5/3/2016, aged 38, the patient suffered the first AMI. In October 2016, the patient suffered a second episode of AMI, performing angioplasty with placement of 2 stents in 2 arteries coronaries. Post-intervention echocardiogram showed 72% LVEF, without alterations. Angioplasty of bifurcation lesion with stent in Anterior Descending Artery (AD) and stent in 1st Diagonal (DG1). Catheterization on 5/4/2017 showed a proximal stent in a lesion of bifurcation, involving DG1, with 80% intra-stent lesion. As for the stent originating from DG1, 90% of the intra-stent lesion was evident. On 05/11/2017, an Intravascular Ultrasound (IVUS) examination showed underexpansion and hyperplasia of both stents. Angioplasty with stent placement was performed pharmacological treatment due to AD artery restenosis, in addition to pharmacological balloon dilation in diagonal branch ostium restenosis. The patient was discharged on 05/13/2017, using ACEI. On 12/23/2017, the patient suffered a new episode of AMI. Transthoracic echocardiogram (ECOTT) showed hypokinesia of the middle segment of the inferolateral wall and basal of the inferior wall. Electrocardiogram showed nonspecific change in ventricular repolarization in V1-V3, DIII and aVF. On 12/24/2017, left main coronary artery without obstructive lesions, AD with 80% lesion intra stent (DIG1 bifurcation), DG1 with 99% lesion intra stent, other arteries unchanged. On 12/29/2017, myocardial revascularization was performed with the left internal mammary in AD and radial artery in DG1 and DG2, with 50 minutes of CPB. On 12/30/2017, ECOTT showed 65% LVEF, hyperdynamic LV with signs of hypovolemia, absence of stroke pericardium and systolic pressure in the pulmonary artery of 29mmHg. Patient was discharged on 02/04/2018. On 03/07/2018, the patient was referred to the hematology service. On 03/28/2018, ECOTT showed LVEF of 56%, akinesia of the inferior septum and inferior wall. Finally, on 5/25/2018, patient is diagnosed with protein S deficiency and C1298A gene polymorphism MTHFR, receiving prescription of Xarelto, AAS and folic acid.

Discussion

The reported case shows the overlapping of two conditions (sickle cell anemia and polymorphism of the MTHFR gene) that increase the chance of a myocardial ischemic event. It is known according to the literature that genetic polymorphisms can aggravate the vaso-occlusive events of sickle cell anemia, leading to ulcer formation, priapism, stroke, avascular necrosis, infarction, and acute chest syndrome [1,4]. In the above case, the patient suffered multiple episodes of AMI, with almost total number of stents. After extensive investigation and assistance from the hematology team, the diagnoses of protein S deficiency and C1298A polymorphism of the MTHFR gene were performed. Is very likely that these newly diagnosed conditions associated with sickle cell anemia have increased the risk of vaso-occlusion and contributed to the patient's episodes of infarction. The causes of hypercoagulability in patients with sickle cell anemia are multifactorial [3]. This hereditary hemoglobinopathy is attributed to a specific molecular lesion, the exchange of glutamic acid for valine at the 6th residue of the hemoglobin beta chain. This results in polymerization of hemoglobin into long fibers forming a gel, transforming the red blood cell more rigid, sickle-shaped and decreasing its flexibility, thus making it difficult to pass through microcirculation. In addition, hyperhomocysteinemia and reduced levels of natural anticoagulants, prevalent in patients with sickle cell anemia, contribute to the thrombus formation [5,6]. The genetic polymorphism A1298C (Glu 429 Ala) of the MTHFR gene, as it was diagnosed in the presented patient, it is associated with a lower activity of the enzyme methylenetetrahydrofolate reductase (MTHFR), responsible for catalyzing the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate (active form of folic acid). That enzyme is necessary for the synthesis of purine and pyrimidine and for the restructuring of methionine from homocysteine [7]. Decreased activity of this enzyme results in elevated levels of homocysteine (hyperhomocysteinemia), which are associated with the onset of cardiovascular complications and possible cause of thrombotic phenomena. Several studies show that damage to the endothelium is one of the mechanisms through which homocysteine leads to vascular injury, via endothelial injury and dysfunction, followed by platelet activation and consequent formation of thrombi, increasing the risk of vaso-occlusion. Hyperhomocysteinemia appears to act as an independent risk factor for arterial endothelial dysfunction, since in experimental models and in cell cultures, this amino acid produced a direct harmful effect on the endothelium [8]. The relationship between folic acid and hyperhomocysteinemia is well demonstrated in the literature and justifies the use of this substance to reduce homocysteine levels. In the study of Framingham, homocysteine, vitamin B12 and folic acid levels of 1,160 patients older than 67 years and a strong inverse re-

lationship was observed between homocysteine and folic acid. The cause of this relationship becomes evident when analyzing the metabolism of homocysteine. One of its metabolic pathways consists of its remethylation, which leads to the formation of methionine. This pathway is dependent on the so-called folate cycle, in which 5-methylenetetrahydrofolate acts as a methyl group donor for homocysteine [9]. So, the folate deficiency causes a decrease in the ability to remethylate homocysteine, leading to its elevation in plasma. With folic acid supplementation, there is an increase in activity of this pathway, being the most effective measure for the reduction of plasmatic homocysteine [10]. The treatment instituted for this patient included folate replacement, to avoid hyperhomocysteinemia and anticoagulation with Rivaroxaban and AAS, to prevent events thromboembolic.

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DOI: 10.32474/ACRR.2023.04.000177