Partial Resolution of Cerebrovascular Stenosis After Conservative Treatment of Moyamoya Disease

Resolução Parcial da Estenose Cerebrovascular da Doença de Moyamoya Após Tratamento Conservador

Mariana Silva Nunes¹
Gustavo Tedde Filho¹
Marcelle Rehem Machado²
Bruno de Sousa Mendes Parente³
Eduardo Waihrich³

RESUMO
Relatamos o caso de um paciente masculino, 28 anos de idade, sem histórico de descendência oriental, que procurou atendimento após apresentar dois quadros de hemiparesia esquerda reversível em um intervalo de seis meses. Lesões isquêmicas não foram evidenciadas nas tomografias computadorizadas (TC) de crânio. O diagnóstico de doença de moyamoya foi confirmado por meio da angiografia cerebral diagnóstica com subtração. A revascularização cirúrgica foi proposta, porém recusada pelo paciente. Iniciou-se tratamento não invasivo com mono-antiagregação plaquetária e rosuvastatina, obtendo-se regressão parcial da estenose.

Palavras-chave: Doença de moyamoya; Rosuvastatina; Tratamento alternativo

ABSTRACT
We report the case of a 28-year-old non-Asian man who attended after having two episodes of reversible left hemiparesis in a period of six months. Ischemic lesions were not found on computed tomography (CT) scans of the brain. The diagnosis of moyamoya disease was confirmed by cerebral digital subtraction angiography. Surgical revascularization was indicated but rejected by the patient. Noninvasive treatment using mono-antiplatelet therapy and rosuvastatin was administered, resulting in partial regression of stenosis.

Keywords: Moyamoya disease; Rosuvastatin; Alternative treatment

INTRODUCTION

Moyamoya disease (MMD) is a chronic occlusive cerebrovascular disorder with high incidence among Asian people. The peaks of age of onset are between 5 and 14 years and at 40 years, and preschool-aged children are most commonly affected. The disease is characterized by internal carotid artery stenosis, often with bilateral involvement. However, pathophysiology is not entirely understood, and diagnostic methods are still limited. Cerebral angiography reveals, in addition to arterial occlusion, a typical pattern known in the literature as “puff of smoke” because of its hazy appearance.

Epidemiological data suggest that 6% of pediatric strokes in the Asian population are caused by MMD and female-to-male ratio is 2:1. Risk factors for the development of MMD include genetic components (10% of cases) related to chromosomes 3, 6, 8, and 17, and secondary causes such as neurofibromatosis type 1, Epstein-Barr infection, tuberous sclerosis, atherosclerosis, leptospirosis, Down syndrome, and hypertension, among others.
A 28-year-old non-Asian brown man with healthy weight and normal levels of cholesterol and triglycerides was seen at the Instituto Hospital de Base, Federal District, Brazil. He had had two episodes of reversible left hemiparesis, the first in February 2016 and the second in September 2016. A computed tomography (CT) scan of the brain showed no acute or chronic ischemic changes. Then, an angiographic study revealed evidence of MMD, including stenosis > 80% in the M1 segment of the middle cerebral artery (MCA), compensatory enlargement of lenticulostriate arteries, and retrograde filling of the MCA territory via pial anastomoses of the anterior cerebral artery (ACA). Low-flow superficial temporal artery MCA M3 segment bypass surgery was indicated, but the patient rejected it. Drug treatment was initiated using mono-antiplatelet therapy with acetylsalicylic acid (ASA) 200 mg/day and rosuvastatin 40 mg/day. Follow up examinations using cerebral angiography were performed in June 2017 and June 2018, showing reduced stenosis, currently at around 50%, with anterograde flow and elimination of retrograde reperfusion. There were no further ischemic events, and motor deficit was completely reversed.

MMD is characterized by progressive stenosis of the terminal branches of the internal carotid arteries and the stem of the MCA and ACA. Etiology remains unknown, but genetic, immune, and inflammatory factors are believed to precede MMD, changing the process of angiogenesis via increased activity of vascular endothelial growth factor (VEGF) and transforming growth factor beta 1 (TGF-beta). Arteries are obstructed by damage to the intimal layer, leading to thrombosis, recurrent transient ischemic attacks (TIAs), and intraparenchymal hemorrhage, which trigger a process of neovascularization of thin and inefficient vessels. Other factors observed in arterial stenosis are a 10-fold increase in basic fibroblast growth factor (bFGF) and increased levels of hepatocyte growth factor (HGF). With regard to genetic factors, a relationship with human leukocyte antigen (HLA) genes is assumed, as well as an abnormal deposition of immunoglobulin G in the inner layers of the vessels.

The clinical picture consists of infarction and ischemia depending on the degree of stenosis and the efficiency of the collateral circulation in promoting blood flow. Thus, ischemic events such as TIA and infarction are more common in children. In the adult population, in turn, hemorrhagic events are more prevalent. Manifestations generally include motor (80.5% of cases) and sensory deficit, choreiform movements, aphasia, focal and generalized seizures (common in children under 5 years of age), headache, cognitive impairment, ischemic stroke, intracranial hemorrhage, and TIA.

Surgical treatment is required, and drugs are usually used as support until the actual surgery. The aim is to provide blood supply to the ischemic region or at risk of ischemia. Revascularization surgery is often used, including superficial temporal artery anastomosis, direct or indirect bypass, and encephalo-duro-arteriosynangiosis. Indirect revascularization is a reliable treatment of choice. Drug treatment usually consists of antiplatelet drugs, steroids, pentoxifylline, and calcium channel blockers.

Following revascularization surgery, 30% of patients with unilateral MMD develop bilateral arteriopathies within approximately 2 years. Monitoring with angiography and magnetic resonance imaging is crucial to avoid future complications. Therefore, it should be used at regular intervals. In surgical revascularization and perfusion of ischemic areas, there is a high chance of immediate postoperative bleeding, which limits the true benefit of ischemic brain revascularization and emphasizes the importance of developing safer surgical techniques to treat these patients or using new medications with higher benefits than surgery.

Regarding pharmacological treatment, ASA does not increase the chance of rebleeding, but there is no evidence of a decrease in the incidence of postoperative ischemic stroke. Long-
term use of antiplatelet drugs is believed to prevent stroke in patients with MMD\textsuperscript{14}. However, some authors report that these drugs are not effective at preventing cerebral infarction or ischemia\textsuperscript{15}. Their argument is based on the theory that ischemia in MMD is mainly due to hemodynamic instead of thromboembolic changes. Also, the use of these drugs is believed to increase the risk of hemorrhagic complications\textsuperscript{15}.

In the current clinical case, treatment using mono-antiplatelet therapy combined with high-dose rosuvastatin improved clinical manifestations and follow-up angiography findings. This suggests that rosuvastatin therapy may be effective in the pharmacological treatment of MMD.

Rosuvastatin can regulate oxidative stress because of its anti-inflammatory and antiapoptotic effects\textsuperscript{16}. The pleiotropic effect of statins induces a reduction in levels of C-reactive protein and proinflammatory cytokines interleukin (IL)-1, IL6, and TNF-alpha. In addition, statins improve nitric oxide bioavailability and reduce nuclear factor-\kappa B activation, showing anti-inflammatory and vasodilatory effects\textsuperscript{17}.

We believe that these anti-inflammatory properties and an improved hemodynamic environment in cerebral circulation, in patients with MMD, could lead to reduced disease progression or even, as observed in our clinical case, regression of endothelial lesions.

**CONCLUSION**

MMD remains a not fully understood condition whose therapeutic options are limited. Ischemic and hemorrhagic events may have disastrous consequences to patients, including severe neurological impairment. Treatment usually involves antiplatelet therapy up to the time of revascularization surgery. We obtained satisfactory clinical and radiological outcomes, including regression of stenosis and endothelial lesions, as evaluated by serial angiography, after the administration of mono-antiplatelet therapy (i.e., ASA) and rosuvastatin. We believe that the benefits of rosuvastatin use are explained by its neuroprotective and anti-inflammatory effects, leading to hemodynamic improvement in neovascularization.

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**Figure 1.** Tomographic sections at the level of midbrain. A. thalamus; B. caudate nuclei; C. cortex; D. no ischemic lesions.
Figure 2. Angiogram, oblique view: A. early arterial phase; B. middle arterial phase; and C. late arterial phase, before rosuvastatin treatment. Follow up angiogram, oblique view: D. early arterial phase; E. middle arterial phase; and F. late arterial phase, six months after rosuvastatin treatment. There was a significant improvement in anterograde arterial flow and in the arterial tree.

Figure 3. Angiogram, frontal view: A, B. early and late arterial phase, respectively; and C. venous phase, before rosuvastatin treatment. Follow up angiogram, frontal view: D, E. early and late arterial phase, respectively; and F. venous phase, six months after rosuvastatin treatment. There was a significant improvement in anterograde arterial flow and in the arterial tree. Comparing images C and F the absence of retrograde collateral flow in the venous phase in the middle cerebral artery territory is seen, as after treatment blood flow became completely anterograde.
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CORRESPONDING AUTHOR

Gustavo Tedde Filho
Medical student
Centro Universitário de Brasília (UniCEUB)
Brasília, DF, Brazil
E-mail: gustavo.gtf@hotmail.com

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Institution: Instituto Hospital de Base do Distrito Federal, Brasília, DF, Brazil.