Bilateral Ischemic Strokes Secondary to Moyamoya Syndrome Associated With Graves Thyrotoxicosis in a Patient of Amerindian Descent From Peru: A Case Report

Jorge Ramírez-Quiñones, Sarah Wahlster, Danny Barrientos-Imán, Ricardo Otiniano-Sifuentes, Pilar Calle-La Rosa, Ana Valencia-Chávez, Carlos Abanto-Argomodo.

Abstract

Moyamoya disease (MMD) is characterized by progressive stenosis of the distal portion of the internal carotid artery and its two main branches, the middle cerebral artery, and the anterior cerebral artery. Clinically, MMD can present with ischemic or hemorrhagic cerebrovascular events. The term Moyamoya syndrome (MMS) is used when the characteristic Moyamoya vasculopathy presents in association with other conditions such as Graves’ disease (GD). We report a case of a 34-year-old, right-handed male patient of Amerindian descent. He presented to the emergency room with a two-month history of palpitation, fatig...
occlusion of the right MCA in its proximal portion and significant stenosis of the ICA and ipsilateral ACA; and significant stenosis in the left ICA, ACA, and MCA (Figure 2E). The digital subtraction angiography in the right carotid axis showed stenosis of the ICA (supraclinoid segment), stenosis of the A1 segment of the ACA, and absence of representation of the MCA (Figures 3A-3B), and in the left carotid axis, it showed stenosis of the ICA (supraclinoid segment), ACA segment A1 stenosis and MCA segment M1 stenosis (Figure 3C). No pathological changes were noted in the vertebrobasilar territory. Transthoracic echocardiography, 24-hour Holter, and carotid duplex studies did not show any abnormalities. The diagnosis was bilateral cerebral infarction due to MMS associated with thyrotoxicosis due to GD. Treatment was started with acetylsalicylic acid 100 mg per day, atorvastatin 80 mg per day, and methimazole 30 mg per day (divided into three doses) while no surgical revascularization was performed. At the three-month follow-up, the patient’s neurological exam had improved with a residual minor hemiparesis; the mRS score was 2.

| Parameter                          | Patient     | Reference values |
|------------------------------------|-------------|------------------|
| Thyroid-stimulating hormone - TSH  | <0.005 IU/ml| 0.3-5 IU/ml      |
| Free thyroxine - FT4               | 6.13 ng/dl  | 0.9-1.7 ng/dl    |
| Anti-thyroglobulin antibodies      | 474.8 IU/ml | 0-115 IU/ml      |
| Anti-thyroid peroxidase            | 600 IU/ml   | <35 IU/ml        |
| Anti-TSH receptor antibodies       | 5.72 IU/ml  | 0-1.75 IU/ml     |

**TABLE 1: Patient’s complete thyroid panel and reference values**

**FIGURE 1: Brain MRI**

A) FLAIR showing hypersignal in the caudate nucleus, anterior limb of the internal capsule, and right lenticular nucleus, in addition to leptomeningeal enhancement or the "ivy sign" (white arrows). B) DWI showing restricted area. C) DWI with bilateral watershed ischemic areas.

FLAIR: fluid-attenuated inversion recovery; DWI: diffusion-weighted imaging
FIGURE 2: A) TOF MRA showing the absence of flow in the right ICA, MCA, and ACA and decreased flow in the left ICA, MCA, and ACA. B) Angio-tomography with an absence of flow in the right MCA (arrow) and severe stenosis of the left ICA and MCA (arrowhead).

TOF MRA: time of flight magnetic resonance angiography; ICA: internal carotid artery; MCA: middle cerebral artery; ACA: anterior cerebral artery

FIGURE 3: Digital subtraction angiography

(A) Right ICA anteroposterior view with supraclinoid ICA stenosis, ACA A1 stenosis, and absence of MCA representation, also visualizing the posterior communicating artery (arrowhead) and posterior cerebral artery filling. (B) ICA lateral view with an absence of MCA representation. (C) Left ICA anteroposterior view with supraclinoid ICA stenosis, ACA A1 segment, and MCA M1 segment stenosis.

ICA: internal carotid artery; MCA: middle cerebral artery; ACA: anterior cerebral artery

Discussion

The term MMS is used to describe the coexistence of the intracranial vascular abnormalities encountered in MMD with other well-documented conditions such as radiation exposure to the head and neck, trisomy 21, neurofibromatosis type 1, sickle cell anemia, and GD [1,4]. It is postulated that there is a causal association between these conditions and the pathogenesis of intracranial vasculopathy. The coexistence of thyroid disease and MMS was first reported in 1983 at the annual meeting of the Japanese Neurology Society, which included three cases with typical radiological findings of MMS and elevated levels of thyroid hormones. The association with GD was first published by Kushima et al.’s study on two young Asian women [5]. Most reports come from Asia, three cases have been reported in Latin America so far (all of them female patients): two in Brazil [6] and one in Colombia [7]. To the best of our knowledge, this is the first report of a Peruvian patient with concomitant MMS and GD. Table 2 summarizes the clinical characteristics, radiological and laboratory findings, and management of the cases reported in South America.
|                          | Case 1                  | Case 2                  | Case 3                  | Our case                |
|--------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Sex                      | Female                  | Female                  | Female                  | Male                    |
| Age (years)              | 22                      | 15                      | 27                      | 34                      |
| Previous diagnosis of hyperthyroidism | Yes                     | No                      | Yes                     | No                      |
| Clinical presentation    | Left hemiparesis, Dysarthria, Headache | Altered mental status, Broca's aphasia, Right hemiparesis | Left hemiparesis, Left-sided hypoesthesia | Left hemiparesis, Dysarthria |
| Non-contrast head CT     | Right MCA territory infarction | Left MCA territory infarction | Right MCA territory infarction | Bilateral infarction of MCA territory |
| Digital subtraction angiography (DSA) | Left ICA, MCA, and ACA stenosis. Right MCA occlusion. | Left ICA and MCA stenosis. | Right ICA, MCA, and ACA stenosis. | Right ICA and ACA stenosis. Right MCA occlusion. Left ICA, ACA, and MCA stenosis. |
| Thyroid-stimulating hormone - TSH (Ref.: 0.3-5 IU/ml) | < 0.03 µUI/mL | < 0.03 µUI/mL | 0.05 µUI/mL | <0.005 IU/ml |
| Thyroxine - T4 (Ref.: 4.5 – 13 µg/dl) | 23.4 ug/dl | 22.3 ug/dl | 21.2 ug/dl | NA |
| Free thyroxine - FT4 (Ref.: 0.9-1.7 ng/dl) | NA | NA | 4.09 ng/dl | 6.13 ng/dl |
| Anti-thyroglobulin antibodies | Positive | Negative | NA | Positive |
| Anti-thyroid peroxidase | Positive | Positive | NA | Positive |
| Anti-TSH receptor antibodies | NA | NA | NA | Positive |
| Hypothyroidism management | Propylthiouracil, Propranolol | Propylthiouracil | Methimazole, Propranolol, Radioactive iodine | Methimazole |
| Surgical revascularization | No | No | No | No |

TABLE 2: Clinical characteristics, complementary findings, and management of cases reported in South America with Moyamoya syndrome and Graves’ disease

CT: computed tomography; ICA: internal carotid artery; MCA: middle cerebral artery; ACA: anterior cerebral artery; NA: not available

The pathophysiological mechanisms that are thought to associate GD with MMS include 1) alteration in the regulation of vascular tone due to increased sensitivity of the sympathetic nervous system [8], and 2) altered T-cell dysfunction; both mechanisms are thought to lead to histological changes of the arterial walls with the progressive appearance of subendothelial fibrosis, intimal thickening and proliferation of smooth cells [9], and hemodynamic changes with alteration of vasoreactivity. Furthermore, it has been reported that GD patients develop vascular changes not only in the typical arteries of the MMS but also more so in the proximal portions of the ICA [10-12], suggesting the existence of a predominantly thyroid vasculopathy in the vessels that receive innervation from the superior cervical ganglion [13]. The reason why these arteries are preferentially affected remains unclear.

Unlike our case, patients with GD and MMS are mostly young women of Asian descent between the ages of 29 and 34 years [8,14-15]. As described by Ohba et al. and Chen et al., ischemic cerebrovascular disease (transient ischaemic attack (TIA) or infarction) is the most frequent form of presentation in this form of MMS [8,14], similar to MMD [16]. From the radiological point of view, cortical and subcortical areas dependent on the anterior circulation of the circle of Willis are affected, predominantly involving the territory of the MCA. Less frequently, the territory of the ACA, as well as the watershed territories, are...
affected [14-15]. Our patient’s MRI demonstrated bilateral acute ischemic lesions in the anterior circulation, a rare finding only documented on a few occasions in the literature [13,17-18]. The "ivy sign" was also evidenced in the FLAIR sequence, observed as a leptomeningeal hypersignal [19] due to maximum dilation of the pial vasculature to compensate for the decrease in cerebral perfusion pressure in these areas [20]. Angiography showed bilateral vascular damage similar to that of MMD, a finding present in 79% of reported cases [15]. In addition to the neurological manifestations, our case presented with clinical and laboratory manifestations of thyrotoxicosis (reported in up to 45% of cases) and received a de novo diagnosis of Graves’ disease, as occurred in 23% of cases in the series by Shah et al. [15].

Therapeutic options include a combination of medical and surgical treatments, including direct or indirect revascularization, and anti-thyroid medication. When revascularization is planned, treatment with thyroid suppressing medications is associated with a better short-term functional prognosis and lower incidence of new ischemic infarcts [14,18]. In addition, some patients are treated with propranolol for the management of autonomic symptoms and tremors. Corticosteroids, as well as other immunosuppressive medications, may also be indicated. The comparison of the clinical results of pharmacological management versus pharmacological-surgical management did not show differences although surgical treatment is recommended in patients with unfavorable clinical and radiological evolution [15]. Our case received only anti-thyroid treatment. Disease progression in MMD versus GD-associated MMS is different. Compared with GD patients, in those with MMS and GD, the progression of the stenosis assessed by angiography is more frequent (40% versus 20.7%) and faster (40 versus 59 months) despite anti-thyroid treatment or surgical treatment [8]. Furthermore, fluctuations in thyroid function or states of thyrotoxicosis are associated with cerebrovascualr events due to an increase in brain metabolism and oxygen consumption [8,14-15].

Conclusions

In conclusion, we report the first case from Peru with a diagnosis of MMS associated with GD in a patient of Amerindian descent. Our case contributes to a growing body of literature describing rare presentations of MMS and may inform future studies about the associations between ethnicity and race with this pathology. MMS represents an infrequent cause of ischemic cerebrovascular disease and, the presence of concomitant diseases, such as GD, should be investigated in the appropriate clinical context to guide management and improve the functional prognosis.

This study was approved by the Instituto Nacional de Ciencias Neurológicas Institutional Review Board. Consent was not required for this case report, including de-identified information appropriately compliant with institutional requirements.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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