

Case Report

# Fluctuations in Moyamoya Vasculopathy Associated with Basedow Disease Depending on Thyroid Hormone Status

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## Keywords

Ischemic stroke · Quasi-moyamoya disease · Moyamoya vasculopathy · Basedow disease · Thyrotoxicosis

## Abstract

A 31-year-old woman presented with sudden onset of weakness in her left upper limb. Magnetic resonance imaging revealed acute cerebral infarctions in the right frontal and parietal lobes. Magnetic resonance angiography showed stenosis in the proximal portions of the bilateral middle cerebral arteries and terminal portions of the bilateral internal carotid arteries. The patient also complained of thyrotoxic symptoms, such as tachycardia, goiter, and fine finger tremor. She was diagnosed with acute ischemic stroke due to moyamoya vasculopathy (MMV) associated with Basedow disease. The patient's thyroid hormone status normalized and intracranial artery stenosis gradually improved. However, after 6 months, she developed transient left hemiparesis during the 7th week of gestation. Her thyroid function deteriorated, and MMV

progressed. Then, MMV improved again with the normalization of her thyroid function. This case shows that MMV associated with Basedow disease could worsen or improve depending on the thyroid hormone status.

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## Introduction

Basedow disease is an autoimmune disorder and is the most common cause of hyperthyroidism, which is associated with an increased risk for ischemic stroke among young adults [1]. Several underlying mechanisms have been correlated with this phenomenon, which include atrial fibrillation, antiphospholipid syndrome, cerebral vasospasm, cerebral vasculitis, and quasi-moyamoya disease [2]. Basedow disease is rarely accompanied by moyamoya vasculopathy (MMV); therefore, the underlying pathology, treatment, and prognosis of such condition has not been fully elucidated.

Herein, we present a patient who developed recurrent acute ischemic stroke with MMV associated with Basedow disease. The condition was characterized by recurring deterioration and improvement of the intracranial artery stenosis that is dependent on the thyroid hormone status.

## Case Report

A 31-year-old woman was admitted to our hospital due to sudden weakness in the left upper limb. She had experienced transient weakness in her left hand 7 days earlier and transient numbness in the left side of her face 3 days earlier. No significant findings were obtained based on her medical history, except for appendectomy due to appendicitis at the age of 20 years. She had taken oral contraceptives and smoked two packs of cigarettes a day. Her family history was noncontributory.

Physical examination revealed tachycardia, diffuse goiter, fine finger tremor, and excessive sweating. She was alert and had mild left hemiparesis (manual muscle test: 4/5 in both arms and legs) and left hand hypesthesia. Other neurological examination results were normal. Moreover, complete blood count, serum chemistry, and coagulation test findings were normal. She presented with high levels of free triiodothyronine at 12.30 pg/mL and free thyroxine (fT<sub>4</sub>) at 3.04 ng/dL and low levels of thyroid-stimulating hormone (TSH) at 0.00 μIU/mL. The patient tested positive for thyroid autoantibody including TSH-stimulating antibody, but not for antinuclear antibody and perinuclear and cytoplasmic antineutrophil cytoplasmic antibody.

Electrocardiography, Holter electrocardiography, and transthoracic echocardiography did not show any abnormalities. Thyroid ultrasonography revealed diffuse goiter with hypervascularity. Magnetic resonance imaging (MRI) showed acute cerebral infarctions in the right frontal and parietal lobes (Fig. 1a). Magnetic resonance angiography (MRA) revealed stenosis in the proximal portions of the bilateral middle cerebral arteries (MCAs) and the terminal portions of the bilateral internal carotid arteries (ICAs) (Fig. 1b, 2a). Conventional cerebral angiography using iodine contrast agent was not performed, because the patient presented with

thyrotoxicosis. SPECT (single-photon emission tomography) showed decreased cerebral blood flow in the right MCA territory (Fig. 1c).

The patient was then diagnosed with acute ischemic stroke with MMV and thyrotoxicosis due to Basedow disease. We administered aspirin and cilostazol orally and argatroban and edaravone intravenously. The use of oral contraceptives was discontinued, and thiamazole and potassium iodide were initiated for the treatment of Basedow disease. Her clinical symptoms disappeared on the 3rd day of hospitalization, and she was discharged from the hospital on the 18th day of hospitalization. The use of medications, such as cilostazol and thiamazole, was continued.

She became euthyroid after 2 months, and MRA showed improvement in intracranial artery stenosis to some extent (Fig. 2b). Four months later, further improvement was observed on MRA (Fig. 2c), and conventional cerebral angiography showed mild stenosis of MCAs without the presence of moyamoya vessels at the base of the brain. SPECT did not reveal any abnormalities, thereby indicating an improvement in cerebral blood flow in the right MCA territory. Six months later, she developed transient left hemiparesis during the 7th week of gestation. Laboratory test results showed deterioration of thyroid function (fT<sub>4</sub> level of 1.77 ng/dL and TSH level of 0.00 μIU/mL). MRI did not show any infarctions; however, MRA revealed slight re-stenosis of the bilateral MCAs (Fig. 2d). She became euthyroid after 3 weeks and underwent artificial abortion.

After a month of transient ischemic attack, a week after she had become euthyroid, MRA showed progression of bilateral MCA stenosis (Fig. 2e), and high-resolution, black-blood T1-weighted MRI with fat suppression did not reveal wall thickening of the stenosed MCAs (Fig. 3). MRA after 3 months of transient ischemic attack again showed improvement of the MCA stenosis (Fig. 2f).

## Discussion

This case was characterized by repeated ischemic stroke with progression of MMV during thyrotoxicosis. The patient presented with severe stenosis in the distal ICAs and proximal MCAs, and these angiographic findings corresponded to MMV. We could not perform conventional cerebral angiography during the acute period due to thyrotoxicosis; therefore, the presence of moyamoya vessels was not accurately evaluated. Unexpectedly, intracranial artery stenosis gradually improved after a few months with the treatment of thyrotoxicosis. Moyamoya vessels were not observed on cerebral angiography performed during the chronic period when MMV almost improved. Therefore, we could not make a diagnosis of quasi-moyamoya disease without evidence of moyamoya vessels and used MMV to describe the morphological change of the intracranial arteries in this patient. Notably, the MMV-associated Basedow disease progressed during thyrotoxicosis and improved with normalization of the thyroid hormone status in our case.

Although Basedow disease is rarely complicated by MMV, Basedow-related MMV (Bas-MMV) usually occurs in young women during thyrotoxicosis. Revascularization surgery is occasionally required for Bas-MMV during the acute period of ischemic stroke [3]. However, the prognosis of Bas-MMV has not been fully elucidated, and such a condition may not always progress, unlike moyamoya disease. Table 1 shows a summary of 6 case reports [4–9] which

showed improvement in Bas-MMV during the clinical course. Three patients (cases 1–3) and the patient in this case report were treated with an antithyroid drug [4–6], and 1 patient (case 4) was treated with an antithyroid drug and angioplasty [7]. The remaining 2 patients (cases 5 and 6) were treated with antithyroid and immunosuppressive agents [8, 9]. In cases 1–3 and our case, Bas-MMV improved after a few months, and residual stenosis was more likely to be observed [4–6]. In case 4, the patient was treated via angioplasty using verapamil during the acute phase of ischemic stroke, and improvement in MMV to some extent was observed. Moreover, the patient completely recovered after 6 weeks [7]. This case shows that Bas-MMV might be at least partially caused by vasospasm. In case 6, methylprednisolone, in addition to an antithyroid drug, was used because wall thickening of the stenotic vessels was observed with gadolinium enhancement [9]. It was assumed that cerebral vasculitis was the underlying pathogenesis in this case.

The pathogenesis of Bas-MMV is not fully understood; however, some mechanisms are associated with this condition. Numerous case reports of coronary artery spasm in Basedow disease are available [10], and the study by Oh et al. [7] has shown that Bas-MMV can also be caused at least in part by vasospasm. It is hypothesized that the activation of sympathetic nerves through hyperthyroidism induces vasospasm. Cerebral arteries are innervated by sympathetic nerves containing noradrenaline and 5-hydroxytryptamine, and excess catecholamine levels or sensitivity due to thyrotoxicosis can lead to vasospasm [11]. Moreover, vascular contractile responses to norepinephrine were greater in large vessels than in small ones [12]. This fact may explain the stenosis in large arteries, such as the ICA or MCA, in Bas-MMV.

However, vasospasm may not fully explain the vascular morphological change in Bas-MMV, because arterial stenosis improved a few months after normalization of the thyroid hormone status, and, subsequently, residual stenosis was usually observed. Gon et al. [13] and Ito et al. [9] have reported that arterial wall thickness in Bas-MMV was observed in imaging studies with gadolinium enhancement. The latter study used methylprednisolone and achieved good recovery of Bas-MMV [9]. Thus, both artery spasm and an immunological mechanism might be associated with morphological change in the cerebral arteries in Bas-MMV; however, further studies must be conducted to accurately determine the etiology.

In our case, oral contraceptives and smoking could have been associated with the first ischemic stroke and pregnancy with the second one. Increased serum estrogen levels due to the use of oral contraceptives or pregnancy can increase the risk of ischemic events. Human chorionic gonadotropin produced during pregnancy also has a thyroid-stimulating effect [14], and it is associated with the progression of Basedow disease. In addition to Bas-MMV, cerebral hemodynamic changes due to thyrotoxicosis might be associated with the occurrence of ischemic stroke [15].

Herein, we presented a patient who developed acute ischemic stroke with progression of Bas-MMV during thyrotoxicosis. The patient almost recovered with normalization of the thyroid hormone status after a few months. Although various mechanisms are associated with this condition, appropriate treatment for Bas-MMV is not fully elucidated. In some cases, patients with Bas-MMV can recover with treatment for thyrotoxicosis. Revascularization surgery should not be considered unless the cerebral artery steno-occlusive lesions remain even after appropriate antithyroid treatment.

### Statement of Ethics

Our subject has given her written informed consent to publish the manuscript. There is no information revealing the subject's identity.

### Disclosure Statement

The authors have no conflicts of interest to declare.

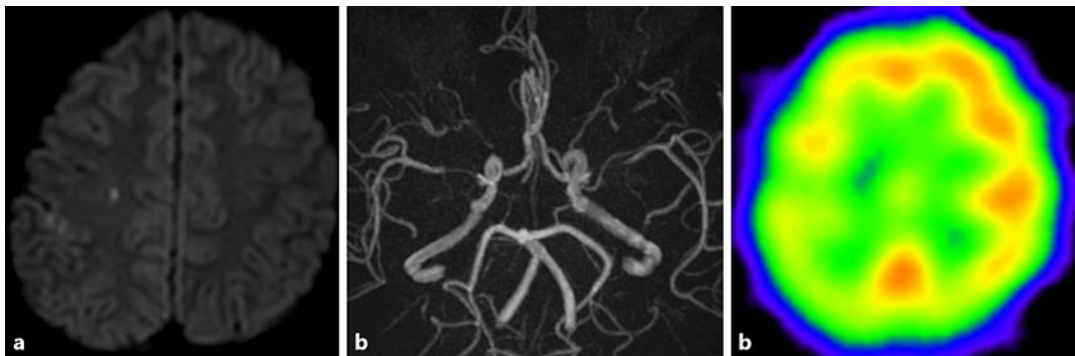
### Author Contributions

Conception and design, acquisition of data, or analysis and interpretation of data: M.H., S.Y., and S.A.; Drafting the article or revising it critically for important intellectual content: M.H., M.O., and T.S.; final approval of the version published: T.K.; agreement to be accountable for the article and to ensure that all questions regarding the accuracy or integrity of the article are investigated and resolved: all authors.

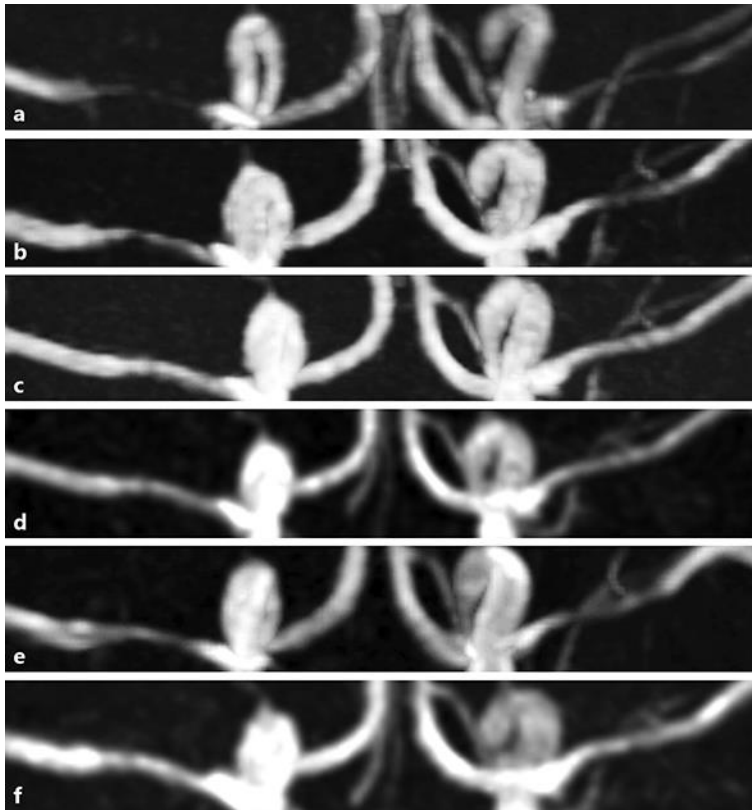
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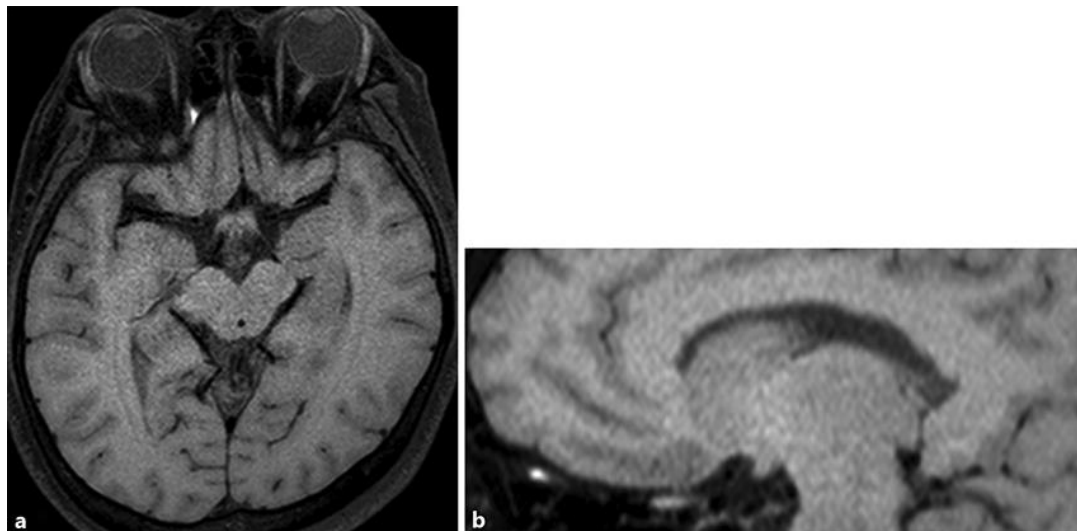
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**Fig. 1.** Magnetic resonance imaging (MRI) and single-photon emission tomography (SPECT) findings during the initial stroke. **a** MRI showed cerebral infarctions in the right frontal and parietal lobes. **b** Left: magnetic resonance angiography revealed stenosis of the proximal portions of the bilateral middle cerebral arteries (MCAs) and the terminal portions of the bilateral internal carotid arteries. Right: SPECT showed decreased cerebral blood flow in the right MCA territory.



**Fig. 2.** Brain magnetic resonance angiography (MRA) during the clinical course. **a** Initial MRA revealed stenosis in the proximal portions of the bilateral middle cerebral arteries (MCAs). **b** Two months later, bilateral MCA stenosis improved to some extent. **c** Four months later, further improvement was observed. **d** Six months later, the patient developed transient left hemiparesis, and slight re-stenosis of MCAs was observed. **e** Seven months later, a week after the patient had become euthyroid, bilateral MCA stenosis worsened. **f** Nine months later, bilateral MCA stenosis improved again.



**Fig. 3.** High-resolution, black-blood fat-suppressed pre-contrast T1-weighted images 7 months after the initial stroke (1 month after the 2nd ischemic event). **a, b** Long and short axial images revealing the absence of thickening in the vessel wall of the stenosed middle cerebral arteries.

**Table 1.** Summary of 6 case reports which showed improvement in Basedow-related MMV during the clinical course

Case No.	Ref. No.	Age, years/ sex	Symptoms	Stroke type	Steno-occlusive lesions	Thyrotoxicosis	Therapy	2nd angiography (pe- riod, finding)	3rd angiography (period, finding)	Residual stenosis
1	4	19/F	headache	hemorrhagic	bil ICAs/MCAs/ACAs	+	AT alone	1 m, improved	1 y, further improved	+
2	5	29/F	transient aphagia, numbness of limbs	ischemic	bil ICAs/MCAs/ACAs	+	AT, AP	6 m, improved	–	+
3	6	26/F	lt hemiparesis	ischemic	rt ICA/bil ECAs	+	AT, AP	6 m, improved	–	NM
4	7	30/F	cortical blindness	ischemic	bil ICAs/MCAs/ACAs/PCAs	–	AT, angioplasty	2 d, improved	6 w, recovery	–
5	8	45/F	consciousness disturbance, rt hemiparesis	ischemic	bil MCAs/ACAs/PCAs	+	AT, mPSL, plasma pheresis	4 m, improved	–	–
6	9	37/F	paresis of rt arm	ischemic	none	+	AT, mPSL, AP	5 m, TIA, stenosis of lt ICA/MCA/ACA	18 m, improved	+
7	this case	31/F	lt hemiparesis	ischemic	bil ICAs/MCAs	+	AT, AP	2 m, improved	4 m, further improved	+

ACA, anterior cerebral artery; AP, antiplatelet drug; AT, antithyroid drug; bil, bilateral; d, day(s); ECA, external carotid artery; ICA, internal carotid artery; lt, left; MCA, middle cerebral artery; m, month(s); MMV, moyamoya vasculopathy; mPSL, methylprednisolone; NM, not mentioned; PCA, posterior cerebral artery; rt, right; w, week(s); y, year(s).