

Recurrent Stroke in Graves' Disease Associated with Moyamoya Disease And Thyroid Storm

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Abstract: *Moyamoya disease is a cerebrovascular disorder characterized by stenosis or occlusion of the terminal portions of the internal carotid arteries which rarely coexists with Graves' disease. We recently experienced a rare case of Graves' disease accompanied by moyamoya disease that presented as a stroke and recurrent stroke.*

20-year-old female was initially admitted to our hospital because of throat discomfort and dysphonia that had developed 5 days previously. She had suffered from hyperthyroidism for 3 years and had a history of irregular medication. After laboratory tests and imaging, she was diagnosed with an acute ischemic stroke associated with moyamoya disease accompanied by Graves' disease. She was prescribed an antithyroid drug (ATD) with an anti-platelet agent. During follow up, she stopped taking the anti-platelet agent and took the ATD. She was re-admitted to the hospital because of a thyroid storm caused by colitis and during admission she developed sudden left hemiplegia, aponia and aphasia. She was diagnosed with an acute ischemic stroke of the right middle cerebral artery (MCA) territory associated with moyamoya disease accompanied by thyroid storm. After anticoagulation and anti-platelet therapy with an ATD, the patient's left hemiplegia improved, however her aponia and dysphasia did not. Thereafter, radioiodine ablation of the thyroid gland was performed. She has been on the medications of Synthroid and cilostazol with tubal feeding via percutaneous endoscopic gastrostomy (PEG) and followed for two years without recurrence of stroke or hyperthyroidism. This is the only and most severe case of recurrent stroke associated with moyamoya disease accompanied by Graves' disease in the literature and gives us the suggestion of using an anti-platelet agent and early ablative treatment for Graves' disease.

Coexistence of moyamoya disease and Graves' disease is rare, although patients with Graves' disease are more likely to develop moyamoya disease. The coexistence of both diseases is believed to be associated with immunological abnormalities and thyroid hormone excess. Clinical manifestations of moyamoya disease associated with Graves' disease are slightly different from the classical moyamoya disease, therefore careful observation and modification of treatment might be needed to treat such patients. However, there have only been a few reported cases and there are no generalized guidelines for treating patients with both diseases.

The authors experienced an extremely rare case of recurrent ischemic stroke with permanent sequela of aponia and aphasia in a young woman with uncontrolled Graves' disease coexisting with moyamoya disease in the absence of other risk factors associated with atherosclerosis or hypercoagulability. Our experience offers suggestions for the management of moyamoya disease presenting as ischemic stroke in combination with Graves' disease. Here we report on this case along with a review of the literature on the coexistence of these diseases.

I. Case presentation

A 20-year-old female initially visited our hospital because of throat discomfort and dysphonia that had developed 5 days previously. She had suffered from Graves' disease and recurrent unexplained headaches for 3 years and had a history of irregular medication. A physical examination revealed anterior neck swelling with exophthalmos. Her vital signs were stable. A blood examination showed suppressed thyroid stimulating hormone (TSH) levels and elevated triiodothyronine (T3) and free thyroxine (FT4) levels. She was positive for anti-thyrotropin receptor antibody (TRAB), anti-microsomal antibody and anti-thyroglobulin antibody. Other blood tests including a coagulation test were non-specific. A brain magnetic resonance imaging (MRI) scan showed a focal hyperintense lesion in the left frontal cortex and deep white matter in the middle cerebral artery (MCA) territory along with a decreased diffusion coefficient in the lesion (Fig. 1. A). A four-vessel cerebral angiogram following left internal carotid arterial (ICA) injection showed severe stenosis involving the cavernous portion with collateral vessels giving the puff of smoke appearance of moyamoya disease (Fig. 2). She was diagnosed with an acute ischemic stroke associated with moyamoya disease accompanied by Graves' disease. She was prescribed 20 mg per day of methimazole and 200 mg per day of the anti-platelet agent cilostazol. The symptoms of cerebral ischemia presenting as dysphonia and headache improved progressively

thereafter. Because of the increased risk of hemorrhage in moyamoya disease, treatment with the anti-platelet agent cilostazol was stopped after resolution of ischemic symptoms and dysphonia and improvement in thyroid function two months after the acute cerebral infarction.

The patient in this case was later transferred to our emergency department (ED) because of abdominal pain and diarrhea combined with fever that had lasted four months after initial admission. She had stopped cilostazol treatment 40 days previously as directed by a doctor and took methimazole irregularly but stopped arbitrarily two weeks prior. On physical examination, she was revealed to have anterior neck swelling, tenderness in the epigastrium and right lower abdomen and no focal neurologic abnormalities. Her body temperature was 39.9°C, heart rate was 130 beats/min, and blood pressure was 140/90 mmHg. Biochemical tests showed leukocytosis with neutrophilia. Liver and renal function tests were unremarkable. Blood tests for thyroid function revealed levels of FT4 7.73 ng/dL (reference value, 0.78 - 1.54 ng/dL), T3 336 ng/dL (reference value, 65 - 150 ng/dL), and TSH 0.009 µU/mL (reference value, 0.55 - 4.78 µU/mL). A diffuse edema was observed in the entire colon by an abdominal computed tomography (CT) scan. She was diagnosed with thyroid storm complicated by acute colitis and was given prompt medical treatment for colitis (intravenous antibiotics with ciprofloxacin and hydration) and thyroid storm (oral propylthiouracil, Lugol's solution, and intravenous beta-blocker). Following treatment, the patient had progressive improvement in vital signs and diarrhea.

However, on the second day after admission, the patient showed sudden left hemiplegia, aphonia and aphasia. An emergent diffusion MRI revealed multifocal hyperintense lesions predominantly involving the right frontal lobe, corpus callosum splenium and temporal lobes with matched decreased diffusion coefficient (Fig. 1. B). Cerebral CT angiography showed stenosis and occlusion of both distal ICAs (Fig. 3) and Diamox single-photon emission computed tomography (SPECT) showed severely decreased perfusion in the right MCA territory and moderately decreased perfusion in the left MCA territory (Fig. 4). She was diagnosed with an acute ischemic stroke in the right MCA territory associated with moyamoya disease accompanied by thyroid storm. Anticoagulation and anti-platelet treatments were initiated and antithyroid drug therapy was continued. Left hemiplegia improved, however aphonia and dysphasia did not, therefore the patient underwent percutaneous endoscopic gastrostomy (PEG) for feeding and voice training. Thereafter, radioiodine ablation of the thyroid gland was performed. She has been on the medications Synthroid and cilostazol with tubal feeding via PEG and followed for two years without recurrence of stroke or hyperthyroidism.

II. Discussion

Moyamoya disease is a chronic and progressive vascular disease caused by stenosis or occlusion of blood vessels around the circle of Willis and shows net-like collaterals on cerebral angiography. It is more commonly diagnosed in Asia and the definite pathogenic mechanism is not known. However, an increased prevalence in specific areas and within families suggests involvement of a genetic cause. Moyamoya disease is typically diagnosed when there is no coexisting systemic disease, however, if there are angiographic abnormalities similar to those of moyamoya disease with causative associated disease, the term "moyamoya syndrome" can be distinctly applied.⁶ Infectious diseases, hematologic diseases such as sickle cell disease and beta thalassemia, connective tissue diseases such as neurofibromatosis 1, and autoimmune diseases such as systemic lupus erythematosus (SLE) and Graves' disease have been reported as associated diseases. Clinical manifestations are variable and can include transient ischemic attack (TIA), ischemic stroke, hemorrhagic stroke and epilepsy. Clinical presentation is different depending on region and patient age. In China and Taiwan, intracerebral hemorrhage is the dominant presentation,¹ however, ischemic stroke is a more common clinical manifestation in western countries.^{4,5} Generally, bleeding tendency is increased in patients older than 10 years old, therefore hemiparesis and seizures caused by cerebral infarction are common in children, while headache and loss of consciousness caused by cerebral hemorrhage are common presenting features in adults with moyamoya disease.^{2,3}

The patient in this case initially developed ischemic stroke at a very young age without known risk factors of hypercoagulability or atherosclerosis and with no family history of ischemic stroke or moyamoya disease. Coexistence of Graves' disease is a potential triggering factor for developing moyamoya vessels and resultant ischemic stroke. An antithyroid drug (ATD) and an anti-platelet agent were prescribed. The pathogenic mechanism for the development of moyamoya disease associated with Graves' disease is unknown. These two disease entities can coincide by chance, however several mechanisms have been suggested to link these two diseases. First of all, both diseases are associated with T-cell mediated immunity. Because of this, an immunologic mechanism has been hypothesized due to the dysregulated immunologic stimulation of the thyroid gland in Graves' disease which shares a pathogenic link with the cellular proliferation and vascular abnormalities of moyamoya disease.⁷ Second, hyperthyroxinemia itself can cause vascular hyperactivity to sympathetic stimulation and resultant pathologic changes of the vascular wall leading to vascular occlusion.⁸ Moreover, hyperhomocysteinemia associated with thyrotoxicosis can aggravate atherosclerosis and increase the risk of thrombosis. ⁹

Bleeding is a common clinical presentation in adult patients with moyamoya disease, however, moyamoya disease associated with Graves' disease is expressed as TIA or ischemic stroke, and thyroid function at presentation is thyrotoxic in most cases.¹⁰ Most of these patients recovered from the neurologic symptoms within several months after treatment. Ischemia associated symptoms improved in parallel with the improvement in thyroid function and the treatment outcomes were similar in patients treated by antithyroid therapy with or without surgery. Therefore, good control of thyroid function is important for treatment. Based on the review of the literature, in one case there was a relapse of ischemic stroke and thyrotoxicosis after revascularization surgery and treatment with Logol's solution instead of ATD because of associated agranulocytosis. After a second operation was performed in the euthyroid state following radioiodine treatment, the patient recovered completely.¹¹

Our patient was treated with an ATD and an anti-platelet agent after the first ischemic attack. However, after improvement in thyroid function, she was treated only by the ATD. During thyroid storm caused by irregular medication complicated with acute colitis, the patient developed recurrent ischemic stroke. Thyroid storm is an extreme condition of thyrotoxicosis and the risk of ischemic stroke may be increased because of hemodynamic instability and sympathetic hyperactivity. After recurrent ischemic stroke during thyroid storm, our patient did not recover completely and permanent disabilities including aphonia and dysphagia remained, which are the poorest outcomes reported in the literature.

Our case suggests that moyamoya disease associated with Graves' disease predominantly presents as ischemic stroke, and the risk of recurrent ischemia increases following worsening of thyroid function. Therefore, maintenance with anti-platelet therapy seems to be beneficial until the normalization of thyroid function, even though it may increase the risk of hemorrhage. In addition, early radical treatments for the thyroid gland such as radioactive iodine ablation or surgery should be considered to stabilize thyroid function if the patient has poor compliance with ATD therapy.

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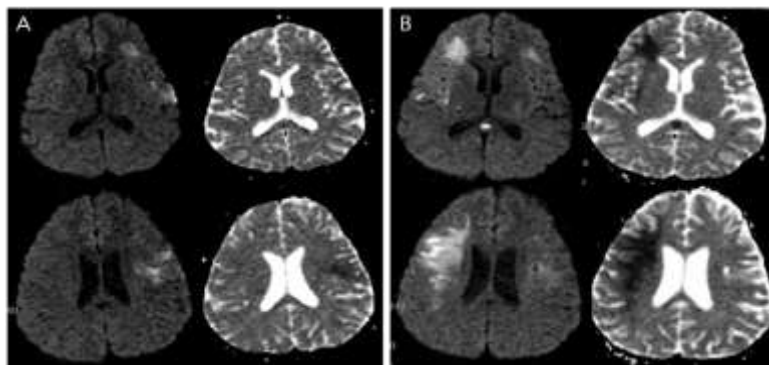


Fig. 1. Diffusion weighted MR imaging after the first (A) and second (B) ischemic stroke.

After the first stroke (A), DWI shows focal hyperintense lesions involving the left frontal and temporal regions which are the middle cerebral artery (MCA) distribution areas, and the apparent diffusion coefficients (ADC) map shows a decreased diffusion coefficient in the lesion. These findings are consistent with an acute cerebral infarction. After the second stroke (B), DWI shows multifocal hyperintense lesions involving predominantly the right frontal lobe, corpus callosum splenium and temporal lobes lateral to the basal ganglia. The ADC map shows a decreased diffusion coefficient in the matched lesions, consistent with an acute cerebral infarction.

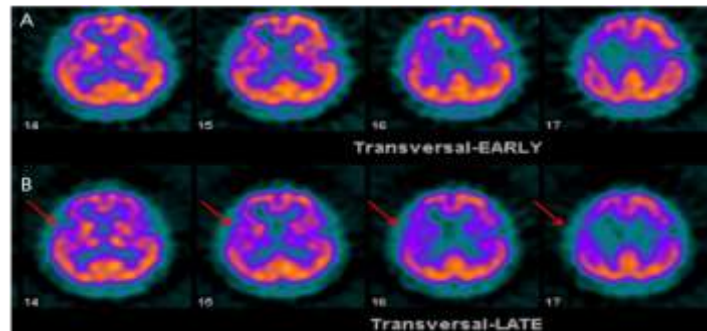


Fig. 2. Diamox enhanced brain perfusion single-photon emission computed tomography (Diamox SPECT).

Basal SPECT (A) shows a moderate to severe perfusion decrease in the right MCA territory and a perfusion defect in the left frontal cortex. Diamox SPECT (B) shows severely decreased perfusion in the right MCA territory (red arrows) and a mild to moderately decreased perfusion reserve in the left MCA territory, suggesting ischemia and a decreased vascular reserve at both MCA territories, predominantly on the right.

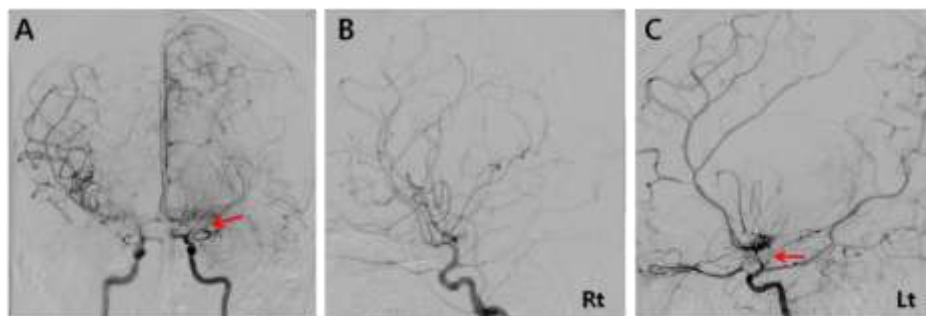


Fig. 3. Four-vessel cerebral angiogram (injection of both internal carotid arteries).

Left internal carotid artery injection (A, C) shows severe stenosis (red arrow) involving the cavernous portion with collateral vessels giving the puff of smoke appearance of moyamoya disease.



Fig. 4. Computed tomography (CT) angiography.

A CT angiogram of the circle of Willis was made using a 3D volume rendering workstation. There is evidence of significant stenosis and occlusion of both distal ICAs in the supraclinoid portion. The vertebro-basilar arteries are well opacified.