



CASE REPORT

Acute Cerebral Infarction in Moyamoya Disease Related with Graves's Disease

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Abstract

A 35-year old man was admitted to the hospital due to Bell's palsy and articulation disorder. Tests revealed that the patient had Moyamoya disease and suffered from cerebral infarction, and that Graves' disease was accompanied. The patient was stabilized after receiving treatments for cerebral infarction and thyrotoxicosis in parallel. Graves' disease is known to cause ischemic stroke in Moyamoya patients via diverse mechanisms, and accordingly, Moyamoya patients with cerebral infarction should be tested for thyroid functions. If a thyroid-related disorder is confirmed, the condition should be thoroughly managed.

Introduction

Moyamoya disease is a disorder where stenosis progresses to occlusion in the peripheries of the bilateral carotid arteries that supply blood to the brain. As the disease progresses, gradual stenosis and occlusion in the middle cerebral artery (MCA) and anterior cerebral artery (ACA) occurs. In addition, to compensate for a reduction of anterior blood circulation in the brain as the blood vessels narrow, abnormal collateral arteries develop near the apex of the carotid artery, cortical surface area, or the leptomeninges, and the external carotid artery bifurcates to supply blood to the dura and the skull base. Moyamoya disease, once progressed, can cause cerebral ischemia, intracranial hemorrhage, headache, movement disorder, seizure, visual field defect, cognitive disorder, etc. Radiotherapy of the head and neck, Down's syndrome, neurofibromatosis type 1, sickle cell disease, and such have been reported to be associated with Moyamoya disease. In addition, hyperthyroidism was reported to co-occur with the disease, although it is very rare [1]. In this article, the authors report a Moyamoya patient, who is believed to suffer from acute cerebral infarction due to Graves' disease accompanying hyperthyroidism.

Case report

A 35-year old man visited the outpatient neurology clinic due to palsy affecting the right side of his face and articulation disorder, which suddenly occurred at work two weeks prior. He was diagnosed as hypertensive in his 20s, but did not undergo detailed tests for the condition or take any medication. He did not have a disease history other than hypertension, or any history of taking medications, drinking, and smoking. At the time of the outpatient clinic visit, his blood pressure was

140/80 mmHg and heart rate was 78, both measured after a 10-minute rest period. The Bell's palsy that had occurred two weeks prior was stable; neither worsening or improving. He did not develop dizziness, dysphagia, or weakness or abnormal sensation in the limbs. No abnormal finding was observed in the physical examination, and the patient was alert according to neurological examination. Light reflex was normal bilaterally and there was no restriction in eye movement. Central facial palsy in the lower right side of his face and articulation disorder were present, but the tongue was not displaced. Muscle strength and sensation of the limbs were normal, deep tendon reflexes were not hyperreflexia or abnormal, and cerebellar function test results were also normal. After being admitted to the hospital, the patient underwent brain MRI, blood testing, electrocardiogram (ECG), and chest radiographs to test for central nervous system disorders. ECG and chest radiograph results were normal. However, brain diffusion weighted image (DWI) showed multifocal high signal intensity in the bilateral frontoparietal cortices and white matter. Additionally, low signal intensity was observed in the corresponding regions on apparent diffusion coefficient (ADC) map (Figure 1), while high signal intensity was observed in fluid-attenuated inversion recovery (FLAIR) image, suggesting the finding of multiple infarcts in the bilateral frontoparietal lobes. Brain magnetic resonance angiography (MRA) showed findings of complete occlusion of the right origin of MCA, and severe stenosis in the proximal and distal regions of the left MCA and in the

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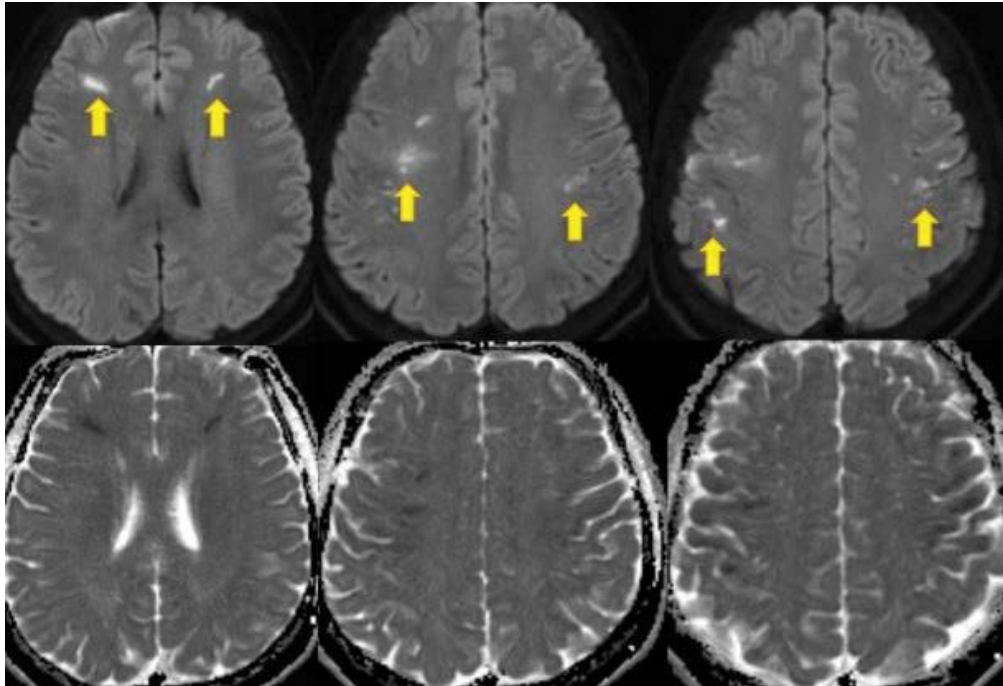


Figure 1: The DWI and ADC map showed a finding suggestive of multifocal cerebral infarcts in the bilateral frontoparietal cortices and white matter.

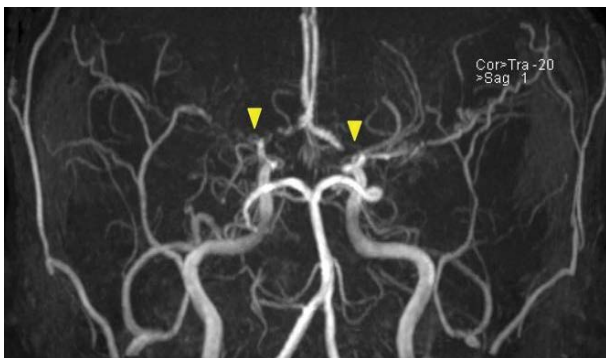


Figure 2: Brain MRA reveals findings of complete occlusion in the origin of the right MCA and severe stenosis and occlusion in the proximal and distal regions of the left MCA and in the origins of the bilateral ACAs.

origins of the bilateral ACAs (Figure 2), i.e., abnormal findings corresponding to Moyamoya disease. Even after admission, the patient's blood pressure consistently read 140/80 mmHg and his heart rate was 70–80 bpm. In 3–4 instances, however, blood pressure elevated to 170/100 mmHg or higher, and heart rate increased to 100 bpm without a specific cause. These symptoms were controlled with the intermittent use of nifedipine, and fever and chills did not occur. Complete blood cell counts, including the peripheral blood smear test, blood chemistry test, and urinalysis were all normal. Factors related to autoimmune diseases and vasculitis (e.g., anti-neutrophil cytoplasmic autoantibodies (ANCA), antinuclear antibody, ESR, CRP, rheumatoid factor, anticardiolipin antibody, lupus anticoagulant, anti-phospholipid antibody, ferritin, and transferrin) were also normal. However, the thyroid function

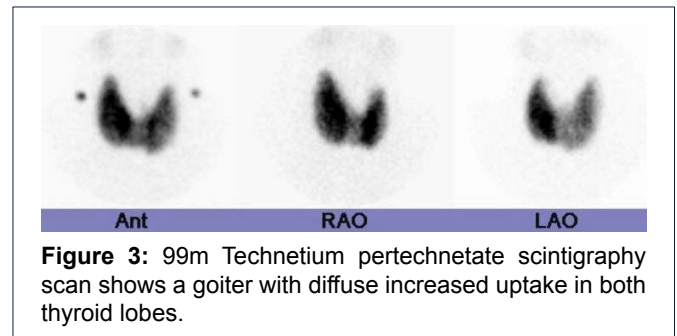


Figure 3: 99m Technetium pertechnetate scintigraphy scan shows a goiter with diffuse increased uptake in both thyroid lobes.

test showed the thyroid stimulating hormone (TSH) to be less than 0.01 μ IU/mL, lower than the normal range (0.55-4.78 μ IU/mL), whereas T3 was 322 ng/dL and free T4 was 3.99 ng/dL, both markedly higher than the normal ranges of 65-150 ng/dL and 0.89-1.76 ng/dL, respectively. In the additional tests related to the thyroid, TSH receptor antibody was 4.97 IU/L (normal range: 0-1.75 IU/L), thyroid microsomal antibody was over 1300 U/mL (normal range: 0-60 U/mL), and thyroglobulin antibody was 481 U/mL (normal range: 0-60 U/ml), showing that all the antibody levels were elevated. According to the thyroid scan, a goiter was observed in the bilateral thyroid lobes (Figure 3). Accordingly, the diagnosis of acute multiple infarcts due to Moyamoya disease was determined, and treatment was initiated with the infusion of isotonic saline solution and administration of an antiplatelet agent. A diagnosis of Graves' disease was also determined in consultation with the Endocrinology Department, and calcium carbonate, cholecalciferol, methimazole, and atenolol were administered. Both echocardiography and 24-hour Holter monitoring were additionally performed to identify that risk factors of the cerebral infarction were normal. After

discharge, the patient continued to take the antiplatelet agent and the treatment for Graves' disease, and was stable without a recurrence of cerebral infarction or a thyrotoxic crisis. Recently, the patient was referred to the Neurosurgery Department to undergo vascular surgery for Moyamoya disease.

Discussion

The cause of Moyamoya disease has not yet been accurately identified, but it has been reported that diverse factors are involved in a complex manner, including bacterial or viral infection, immune and inflammatory responses, genetic factors, autoantibody, and environmental factors. Increased blood flow in the collateral vessel in combination with fragmented elastic lamina, a thinned media in the vessel wall, and microaneurysm of a vessel, were all found in the vessels affected by Moyamoya disease. These symptoms can stress arteries and cause hemorrhages, while multilayered intimal fibrous thickening in vessel walls, over-proliferation of smooth muscle cells, minimal inflammatory cell infiltration, and luminal thrombosis are related to ischemic symptoms [1,2]. Such abnormal proliferation of endothelial and smooth muscle cells has been found to be linked to macrophages and T cells, which can produce angiogenic growth factors and media in Moyamoya patients. It was reported in a study that pathological disorders, including abnormal modulation of T cells, show commonalities with abnormal immunostimulatory causes regarding thyroid functions observed in Graves' disease[3], suggesting the presence of a relationship between Graves' disease and Moyamoya disease. *HLA-Aw24*, *Bw46*, and *Bw54* genes are involved in Moyamoya disease[4] and *HLA-Bw46*, *Bw48*, *DRw8*, *DQw3*, and *DQw4* genes are involved in Graves' disease [5]. Hence, a genetic relevance between the two disorders can be inferred based on the common presence of *HLA-Bw46*.

In the thyrotoxic state, in which thyroid hormones are excessively produced, cerebral metabolism and oxygen consumption increase, which subsequently, reduces cerebral perfusion[6], and increases vessel sensitivity to signals from the sympathetic nervous system [7]. The vessels in the brain areas affected by Moyamoya disease may be constricted which causes cerebral perfusion to decrease, causing infarction. In hyperthyroidism, cardiac output, myocardial contractility, and heart rate increase to match the increased demand for oxygen proportional to the increased metabolic rate. Such increases may lead to a markedly increased diurnal variation of heart rate compared to a normal functioning, increasing the frequency of cardiac dysrhythmia, i.e., a risk factor for ischemic stroke [8]. Furthermore, thyrotoxicosis may elevate methylmalonic acid levels and cause hyperhomocysteinemia, which is known to be strongly associated with atherosclerosis and thrombosis[9], and promotes hypercoagulability in blood [10]. Therefore, considering the previous reports, it is reasoned that Moyamoya disease is related to Graves' disease and that a sudden increase in thyroid hormones due to Graves' disease is highly likely to induce occlusion in the vessels showing severe constriction or hypercoagulability due to Moyamoya disease, or cause

ischemic stroke due to an increased frequency of cardiac dysrhythmia.

The patient in this case study did not have a history of drinking or smoking for a religious reason, and also did not have risk factors of cerebral infarction like hypertension and diabetes. In the blood tests and several other tests performed during his hospital stay to identify risk factors of cerebral infarction, no abnormal findings were observed other than those suggestive of Graves' disease. Considering that his vital signs regular measured during his hospital stay, blood pressure and heart rate intermittently elevated with no specific cause. It is believed that among the several aforementioned mechanisms with which hyperthyroidism may induce cerebral infarction in Moyamoya patients, vasoconstriction due to increased vessel sensitivity to signals from the sympathetic nervous system or temporary change in cardiac output, myocardial contractility, and heart rate was involved in the occurrence of cerebral infarction in this patient.

Graves' disease and Moyamoya disease can co-occur. Thus, in treating patients with Moyamoya disease in whom the occurrence of cerebral infarction is thought to be related to thyrotoxicosis (a condition characterized by an abnormal increase of thyroid hormones) due to Graves' disease, the physician should establish a treatment plan to stabilize thyroid function and prevent thyrotoxicosis from recurring. It should always be kept in mind that treatment to stabilize thyroid function prevents the recurrence and worsening of cerebral infarction, and improves the prognosis of the patient. In addition, it would be valuable to conduct research to investigate whether thyroid function test results, accidentally found in the Moyamoya patient in this case study, can be used as a predictor of ischemic stroke.

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